PORTLAND VETERANS AFFAIRS MEDICAL CENTER

INSTITUTIONAL REVIEW BOARD

Standard Operating Procedures

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—TABLE OF CONTENTS—

APPENDIX P: VHA Directive 2000-043: Banking of Human Research Subjects' Specimens
APPENDIX Q: Humanitarian Use Device Information and Flowchart
APPENDIX R: Planned Emergency Research

I. Introduction

The Portland VA Medical Center Institutional Review Boards' (IRB) Standard Operating Procedures (SOP) for the protection of human subjects in research is a reference for IRB members, IRB Coordinators, investigators, and other individuals associated with the Human Research Protection Program (HRPP). This SOP details the policies and procedures specifying the regulations and policies governing human subjects research and the requirements for submitting research proposals for review by the IRB and the Research & Development Committee.

This document will be reviewed for needed modifications on at least an annual basis to reflect updated and applicable regulations, policies, and institutional procedures.

II. Background

1. Ethical Principles Governing the IRB (Appendix A)

a. VA Research must be carried out in an ethical manner (38CFR16.103(b)(1)). The basic ethical principles governing research involving human subjects are provided in the Nuremberg Code, the Declaration of Helsinki, and the Belmont Report, which are located in Appendix A.

b. **The Nuremberg Code.** The modern history of human subject protections begins with the discovery after World War II of numerous atrocities committed by Nazi doctors in war-related human research experiments. The Nuremberg Military Tribunal developed ten principles as a means of judging their "research" practices, known as *The Nuremberg Code.* The significance of the Code is that it addresses the necessity of requiring the voluntary consent of the human subject and that any individual "who initiates, directs, or engages in the experiment" must bear personal responsibility for ensuring the quality of consent.

c. **The Declaration of Helsinki.** Similar principles to The Nuremberg Code have been articulated and expanded in later codes, such as the World Medical Association *Declaration of Helsinki: Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects (1964, revised 1975, 1983, 1989, 1996, 2000),* which call for prior approval and ongoing monitoring of research by independent ethical review committees.

d. **The Belmont Report.** The Belmont Report contains three basic ethical principles that are central to research involving human research and guide the IRB in assuring that the rights and welfare of subjects are protected. These three principles are:
   (1) **Respect for persons**, which is applied by obtaining informed consent, consideration of privacy, confidentiality, and additional protections for vulnerable populations.
   (2) **Beneficence** is applied so that possible benefits are maximized and possible risks are minimized to the persons involved.
   (3) **Justice** is evidenced in the equitable selection of subjects.

2. The Regulatory Mandate to Protect Human Subjects

The Department of Veterans Affairs (VA) and other Federal regulations require specific protections for human subjects:

a. **Department of Health and Human Services (DHHS) Regulations at 45CFR46**. In January 1991 the VA joined 16 other Executive Branch Departments and Agencies in simultaneously adopting the Federal Policy (Common Rule) for the Protection of Human Subjects. Codified by the VA at 38CFR16, the Common Rule is also codified by the Department of Health and Human Services (DHHS) as Subpart A of the DHHS regulations at 45CFR46. DHHS has three additional Subparts in the regulations, as well, that are not in 38CFR16. **All** human subject research conducted at the PVAMC must adhere to the regulationsat 45CFR46 and 38CFR16.

b. **VA regulations at 38 CFR 16 and the Federal Policy (Common Rule) for the Protection of Human Subjects.**

(1) 38CFR16 – Protection of Human Subjects
(2) 38CFR17.33 - Patients' rights.
(3) 38CFR17.85 - Treatment of research related injuries to human subjects.
(4) 38CFR7.45 - Hospital care in research studies.
(5) 38CFR17.92 - Outpatient care for research studies.

Codified by the VA at 38 CFR 16, the Common Rule is identical to Subpart A of the DHHS regulations, but does not include the additional DHHS Subparts B, C, and D.

c. **Food and Drug Administration (FDA) Regulations**

The following FDA regulations must also be adhered to when appropriate:

(1) 21CFR50 – Protection of Human Subjects
(2) 21CFR56 – Institutional Review Boards
(3) 21CFR54 – Financial Disclosure by Clinical Investigators
(4) 21CFR312 - Investigational New Drugs (IND)
(5) 21CFR314 – Application for FDA Approval to Market a New Drug
(6) 21CFR812 – Investigational Device Exemptions (IDE)

d. **DHHS Office for Human Research Protections (OHRP) – Federal Wide Assurance**

DHHS mandates that every institution conducting human research with federal funds register itself with OHRP and obtain an assurance of compliance approved by the OHRP. Under this OHRP issued Federal Wide Assurance, the IRB that reviews the human research projects is responsible for adhering to and fulfilling the requirements of the Federal regulations of 45CFR46.

A signed copy of the PVAMC FWA may be found in Appendix B.
The Portland VAMC IRBs, abide by the terms set forth in the FWA.
The PVAMC IRB Assurance number is: FWA00000517.
The VA Med Ctr, Portland, OR IRB#1 Registration number is: IRB00001976.
The VA Med Ctr, Portland, OR IRB#2 Registration number is: IRB00003313.
The Community Based Outpatient Clinics identified for this assurance include: Bend, Camp Rilea, Longview, and Salem.

3. **Key Definitions**

- **Conflict of Interest:** a conflict of interest exists when an employee's or group's financial interests or personal obligations may interfere, or appear to interfere, with the employee's or group's professional judgment in conducting, reviewing or reporting research and their obligations to act in the best interest of the PVAMC and without improper bias. The mere appearance of a conflict may be as serious and potentially damaging to the public trust as an actual conflict. Therefore, potential conflicts must be disclosed, evaluated, and managed with the same thoroughness as actual conflicts.
- **Human Biological Specimens**: are defined in the VHA Directive 2000-043 as "any material derived from human subjects, such as blood, urine, tissues, organs, hair, nail clippings, or any other cells or fluids, whether collected for research purposes or as residual specimens from diagnostic, therapeutic, or surgical procedures."
- **Human Subjects**: are defined by the federal regulations [38 CFR 16.102 (f)] as "living individual(s) about whom an investigator conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information."
  The FDA regulations [21CFR56.102(e)] also define a human subject as "an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy individual or a patient."
  The VA Policy (M-3, Part 1, Chapter 9.04.b) definition of human subjects is expanded to include investigators, technicians, and other assisting investigators, when they serve in a "subject" role by being observed, manipulated, or sampled.
- **Individually-identifiable Information**: is any information, including health information maintained by VHA, pertaining to an individual that also identifies the individual and, except for individually-identifiable health information, is retrieved by the individual's name or other unique identifier. Individually-identifiable health information is covered by the Health Insurance Portability and Accountability Act of 1996 (HIPAA), regardless of whether or not the information is retrieved by name. This includes information of the individual which is or may be readily ascertained by the investigator or associated with the information, even through the use of a code book. Typically, "individually identifiable information" is considered to be information that is attached to one or more unique identifiers. The 18 unique identifiers defined through HIPAA are in the HRPP Policy and Procedure No. 6. These include: patient's name, social security number, address, telephone number, etc.
- **Individually-identifiable Health Information:** is a subset of health information, including demographic information collected from an individual, that is: 1) created or received by a health care provider, health plan or health care clearinghouse; 2) relates to the past, present, or future condition of an individual and provision of or payment for health care; and 3) identifies the individual or a reasonable basis exists to believe the information can be used to identify the individual.
- **Institutional Review Board (IRB)**: The IRB is a formally established subcommittee of the Research and Development (R&D) Committee. (M-3, Part 1, Chapter 2.02(e) and 3.01(e)). The IRB, also known as the Subcommittee on Human Studies, is an appropriately constituted group that the VA has formally designated to review and monitor research involving human subjects to protect the rights and welfare of the subjects. The IRB also provides oversight and monitoring of such protections. In accordance with the Common Rule, VA and FDA regulations, the IRB has responsibility for approving, requiring modification (to secure approval), or disapproving research.

- **Legally Authorized Representative**: (M-3, Part 1, Chapter 9.04(a), Oregon Revised Statues 127.635(2)) A legally authorized representative is defined as an individual, or judicial or other body, authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedures(s) involved in the research. For the purposes of this SOP, a "legally authorized representative" includes not only persons appointed as healthcare agents under Durable Powers of Attorney for Health Care (DPAHC), court appointed guardians of the person, but also next of kin in the following order of priority:
  (1) Spouse
  (2) A majority of the adult children (18 years of age or older) who can be so located
  (3) Parent
  (4) A majority of the adult siblings (18 years of age or older) who can be so located
- **Minimal Risk:** (38CFR16.102(i)) a risk is minimal when the probability and magnitude of harm or discomfort anticipated in the proposed research are not greater than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.
- **Private Information:** information that an individual can reasonably expect will not be made public, and information about behavior that an individual can reasonably expect will not be observed or recorded. Private information is information about a patient and/or study participant that is “individually identifiable.” Please see the definition for “identifiable” above.
- **Quorum**: more than half of the voting members of a committee being present and including at least one non-scientist. In order for research to be approved, it must receive the approval of a majority of those members present at the meeting.
- **Research**: is defined by the VA Federal regulations (38 CFR 16.102 (d)) as a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.

  The FDA regulations at 21CFR56.102(c), define research as "...any experiment that involves a test article and one or more human subjects..." The FDA regulations further state that "...the terms research, clinical research, clinical study, study, and clinical investigation are deemed to be synonymous for purposes of this part."

  The Portland VA Medical Center Medical Staff Bylaws define research as an activity designed to develop or contribute to new generalizable knowledge through a process of hypothesis testing and data collection that permits conclusions to be drawn. Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective. Any prospective or retrospective collection of clinical data with the intent to contribute to generalizable knowledge constitutes human studies research. Examples of such clinical data collection include research seminars, posters, abstracts, and manuscripts.

  Local medical center and affiliated institutional conferences for teaching, quality assurance or quality improvement activities, and patient care activities (for example, ward rounds, case conferences, departmental seminars, morbidity & mortality conferences, X-ray conferences, tumor boards) are specifically not considered as research by this definition. Case Reports (published reviews of $\leq$ 3 clinical records by one or more members of the care team) are not considered as research, but do require submission of a Case Report Review application to the IRB Coordinator. Clinical reviews (reviews of $\geq$ 4 clinical records whether or not care team members are involved) are considered human research and must have IRB and Research & Development Committee approval. See also MCM 151-01.

III. Institutional Review Board Administration

1. **The Authority of the IRB (38 CFR 16; 21 CFR 50, 56; and 45 CFR 46).**

The PVAMC IRBs, designated by the PVAMC Director and the R&D Committee (M-3, Part 1, Chapter 2.02 and 3.01), and named in the Federal Wide Assurance (FWA) must prospectively review and make a decision concerning all human subject research conducted at the PVAMC or by PVAMC employees or agents, or otherwise under the auspices of the VA. Further, these IRBs have statutory authority to:

a. take any action necessary to protect the rights and welfare of human subjects in the research program;
b. approve, require modifications in, or disapprove the facility's human subjects research;
c. conduct continuing review of research at intervals appropriate to the degree of risk, but not less than once per year (38 CFR 16.109);
d. suspend or terminate the enrollment and/or ongoing involvement of human subjects in each facility's research as it determines necessary for the protection of those subjects (38 CFR 16.113); and
e. observe and/or monitor the PVAMC's human subject research to whatever extent it considers necessary to protect human subjects.

2. **Purpose of the IRB (38 CFR 16.109).**

The PVAMC IRBs' primary responsibility is to ensure that the rights and welfare of subjects are protected in the VAMC human subject research program (38 CFR 16.109). In doing so, the IRBs must ensure that the human subjects research is conducted ethically, and in compliance with VA and other Federal regulations, the requirements of applicable Oregon and Washington state laws, the PVAMC's Federalwide Assurance (FWA), and the PVAMC's institutional policies and procedures. The IRBs accomplishes prospective and continuing review of the PVAMC's human subject research projects. This includes, but is not limited to, review of the protocol, the informed consent process, and all of the procedures used to enroll subjects.

The review process consists of a review at study inception, and at intervals appropriate to the degree of risk, but not less than once a year.

3. **Shared Responsibilities of the Institution in Protecting Human Subjects**

Although the IRB is a subcommittee of the R&D Committee (M-3, Part 1, Chapter 2.02, 3.01), neither the Medical Center Director nor the designated R&D Committee can approve research involving human subjects that has not been approved by the IRB of record (38 CFR 116.112; M-3, Part 1, Chapter 3.01(e)), nor can it alter an adverse report or recommendation made by the IRB. For example, the disapproval for ethical or legal reasons made by the IRB could not be reversed by the Medical Center Director or R&D Committee.

a. **Medical Center Director (38 CFR 16.112; M-3, Part 1, Chapter 2.02 and 3.01).**

The PVAMC Medical Director is the Signatory Official. The Signatory Official is the official legally authorized to represent the institution under the DHHS approved Federalwide Assurance. The Director is responsible for ensuring compliance with all Federal and VA regulations governing research, for all

research activities conducted under the auspices of the medical center, and is accountable for the Human Research Protection Program (HRPP), including the protection of human research subjects.

The Director reviews and approves all R&D Committee meeting minutes, which includes the R&D review of IRB meeting minutes, and appoints members of the IRB, nominated by the Associate Chief of Staff (ACOS/R&D) and voted on by the R&D Committee.

The Director delegates the authority to administer the Research & Development program to the Associate Chief of Staff/R&D. (M-3, Part I, Chapter 2.02(a)).

b. **Research & Development Committee (M-3, Part I, Chapter 3.01).**
The R&D Committee, which reports to the PVAMC Director, acts as the governing body of the Research Service at the PVAMC. It serves as a parent committee to the IRB and must review and approve IRB actions, minutes, and periodic reports. The R&D Committee is responsible for the scientific quality and appropriateness of all research involving human subjects. All study protocols which have been reviewed and approved by the IRB, must also be reviewed and approved by the R&D Committee, prior to study initiation. The R&D Committee is notified in writing of the IRB decisions regarding each protocol through the IRB meeting minutes, which are submitted to and reviewed by the R&D Committee. The R&D Committee also re-evaluates at least annually the scientific quality of all research studies involving human subjects to assure protection of human subjects.

If, in the course of its review, the R&D Committee requires changes to the protocol that relate to the determination of the protection of the human subjects, the R&D Committees must refer those changes back to the IRB for its approval before the R&D Committee can give final approval.

In addition, the R&D also reviews and evaluates reports and results of compliance assessment and quality improvement activities.

The R&D Committee's Standard Operating Procedures provides additional information regarding the responsibilities and functions of the R&D Committee.

c. **Associate Chief of Staff/Research & Development (ACOS/R&D) Responsibilities. (PVAMC MCM No. 151-01)**
The ACOS/R&D is responsible for:

(1) Developing, managing and evaluating policies and procedures that ensure compliance with all Federal and VA regulations governing research. This includes oversight of all aspects of the Human Research Protection Program (HRPP) established for human research protections. Functionally, this includes the implementation of the HRPP and the monitoring of changes in VA and other Federal regulations and policies that relate to human research protections.
(2) Acting as liaison between the VHA Office of Research and Development and the institution's Research and Development Committee, as well as advising the Director and VISN 20 leadership on key matters regarding research.
(3) Submission, implementation, and maintenance of an approved Federalwide Assurance (FWA) through the medical center Director and the Office of Research Oversight (ORO) (aka Office of Research Compliance and Assurance (ORCA)) and to the Office for Human Research Protections (OHRP).

(4) Administration of the facility's Research and Development Programs, including the Research and Development Committee and applicable subcommittees.
(5) Financial management of the facility's Research and Development Program.
(6) Assisting investigators in their efforts to carry out VA's research mission.
(7) Developing and implementing continuous quality improvement strategies for the purpose of managing risk in the research program. Functionally, this includes ensuring the follow-up on such actions.
(8) Developing training requirements and ensuring that these training requirements, including human, animal, and bio-safety research for investigators and members of the applicable subcommittees and staff are completed.

d. **Administrative Officer/Research & Development (AO/R&D)**

The Administrative Officer (AO) conducts the administrative pre-review of all studies proposed for review by the IRB. The AO must review and approve proposed research projects to assure appropriate facility resources and appropriateness of conducting the study at the PVAMC. This process is achieved through the AO review of the IRB submission requirements completed by the principal investigator, which are included in Appendix C. The PI must submit the Initial Review Questionnaire (IRQ) with all applicable attachments to the IRB Coordinators by the 20th of each month. These materials will be reviewed at the following month's IRB meeting. By signing the "Proposed Project Questionnaire," the AO/R&D acknowledges the resources involved and appropriateness of performing the study at the PVAMC. **Studies which are not approved during the AO review will not be reviewed by the R&D Committee and will not be conducted at the PVAMC.**

In addition, the AO serves as an ex-officio member of the IRB.

e. **The Principal Investigator (M-3, Part 1, Chapter 9.11 & Appendix C, PVAMC MCM No. 151-01).** The IRB recognizes one Principal Investigator (PI) for each project. The Pl has ultimate responsibility for his/her research project. The PI is notified in writing of IRB decisions regarding each protocol. All official IRB correspondence is addressed to the PI, but may be sent to a Study Coordinator as designated by the PI on the Initial Review Questionnaire. In cases where a lapse in time could potentially harm human subjects (such as in the report of an adverse event), Co-Investigators may communicate directly with the IRB.

The **Principal Investigators** (VA, Without Compensation or contract employees) who are planning to conduct human studies research at the PVAMC are responsible for:

(1) Submitting the following applicable forms to the Administrative Officer of Research and Development (R&D) Service prior to submitting a research proposal to a funding agency:
    (a) Proposed Project Questionnaire (PPQ);
    (b) Administrative Review forms;
    (c) Project Proposal and Abstract;
    (d) Institutional Review Board forms, unless exempt from IRB review; and
    (f) Subcommittee on Research Safety forms, if applicable.

These forms should be submitted in a timely manner, which allows thorough review by the AO/R&D. It is recommended that approximately 2 weeks be allowed prior to the funding agency deadline. The forms applicable to the IRB may be obtained from the Research Service office or website:

http://www.visn20.med.va.gov/portlandrd/index.html The IRB forms are located in Appendix C.

(2) Completing all required training for human subject protection prior to submitting a research protocol.

(3) Maintaining credentials and privileges at the Portland VA appropriate for performing all procedures proposed in all research protocols involving human subjects submitted by the principal investigator. If the principal investigator lacks the requisite credentials and privileges, a collaborating VA clinician who is credentialed and privileged appropriately must be listed on the application. The collaborating clinician assumes responsibility for the specific procedures in question.

(4) Obtaining approval from the Portland VAMC Institutional Review Board. As part of the review process, the Principal Investigator must comply with all requests for information to assess conflicts of interest.

(5) Initiating the study only **after** approval has been granted by **both** the Institutional Review Board and the Research and Development Committee. The Research and Development Committee has final responsibility of the scientific quality and appropriateness of all research involving human subjects.

(6) Adhering to all assurances given to the Institutional Review Board at the time the project was approved, and through the duration of the approved protocol. This includes appropriately conducting and documenting the informed consent process, in accordance with the IRB decisions.

(7) Retaining a copy of each signed informed consent form (VA Form 10-1086). The **original** signed consent form must be sent to the Research Service administrative office where procedures are in place to guarantee that it is scanned into the patient's electronic medical record. The original is kept on file in the R&D Service administrative office. A copy must be given to the patient and the patient must initial the original signed consent form acknowledging receipt of a copy of the informed consent form.

(8) Submitting all adverse events occurring in the study to the IRB within the time frame stated on the Adverse Event Reporting form included in Appendix F.

(9) Completing all appropriate annual review forms for continuing review approval of ongoing research to maintain IRB and R&D Committee approval. The Research and Development Committee on an annual basis will assure the scientific quality of each active research protocol.

(10) Submitting annual and continuing reviews of the research project to the R&D Service administrative office according to stated deadlines for entry into the Research & Development Information System (RDIS) database. All required reports will be submitted by the due date(s) specified by the R&D Service administrative office to comply with Federal, VACO and local requirements. These reports may include: proposed changes in research and/or consent forms, deviations from approved protocol, unanticipated problems and termination/completion reports.

(11) Citing in the methods section of all manuscripts involving human studies at the PVAMC that the PVAMC IRB approved the project.

(12) Serving as the VA Responsible Investigator on any research projects undertaken by students, fellows, pre-doctoral trainees and/or interns. This requires the Responsible Investigator with a VA appointment to accept full responsibility for the conduct of the research project.

(13) Submitting questions regarding Institutional Review Board policies and procedures, e.g. questions involving whether or not a project is considered human subjects research

and whether it should be submitted to the IRB for review and approval, in writing to the IRB Coordinators. Once received, the IRB Coordinators will consult with the IRB Members and Chair, if necessary, to address an individual's questions. Investigators should not contact the IRB Members or Chair directly with questions related to IRB policies and procedures. It is the policy of the Portland VA Medical Center IRB to not provide curbside consults to individual investigators and medical staff.

f. **PVAMC Subcommittees**

The R&D Committee may require projects to be reviewed and approved by: the PVAMC Subcommittee of Research Safety (SRS), Institutional Animal Care and Use Committee (IACUC), and/or Subcommittee of Research Space; relevant committees of collaborating institutions and/or by ad hoc reviewers.

g. **Other Institutions.**

The IRB is responsible for the protection of the rights and welfare of human research subjects at the PVAMC and for research conducted under VA auspices. The IRB has no authority over or responsibility for research conducted at other institutions.

h. **Regulatory Agencies.** The IRB and IRB records are subject to regulation and inspection by governmental regulatory agencies (e.g. FDA, Office for Human Research Protections (OHRP), and the VA Office of Human Research Oversight (OHRO). Copies of any applicable reports or correspondence to and from such agencies concerning the PVAMC R&D Committee must be provided by the IRB to the R&D Committee, which shall determine if any additional notifications are necessary.

i. **IRB Staff and Resources.** The IRB has full-time Coordinators, who report to the IRB Chairperson, the AO/R&D, and ACOS/R&D. The Coordinators act as a liaison between the investigators and the IRB. Space for the IRB Coordinators and IRB files is under the purview of the Research Service.

The IRB Coordinators are responsible for:

(1) Maintaining all files, paperwork and correspondence for the IRB.
(2) Notifying the ACOS/R&D if additional resources are needed.
(3) Assigning reviewers for protocols and other materials to be reviewed by the IRB;
(4) Reviewing research proposal submissions, advising Principal Investigators about Federal, VACO, and local requirements for conducting research, placing research proposals on the appropriate subcommittee agenda, and coordinating the final approval by the R&D Committee.
(5) Maintaining subcommittee meeting calendars, minutes, and membership information.
(6) Assisting Principal Investigators who receive approval and funding for research projects with training requirements and assistance with day to day issues of individual research programs.
(7) Completing educational and credentialing requirements, as appropriate.
(8) Responding to requests for consultation, (i.e. questions regarding IRB policies and procedures, e.g. questions involving whether or not a project is considered human subjects research and whether it should be submitted to the IRB for review and approval) from investigator s, research staff, clinicians, etc., received directly from the individual(s) or from the IRB Members and/or Chairs. This includes consulting with the IRB Members and Chairs if necessary to address an individual's questions.

Contact information for the IRB Coordinators is included in Appendix I.

4. IRB Membership (38CFR16.107; M-3, Part 1, Chapter 9.08).

a. **IRB Chairperson**

(1) Appointment

One Chairperson for each IRB is nominated by the ACOS/R&D, voted on by the R&D Committee and formally appointed by the PVAMC Director. The Chair must hold a VA appointment.

(2) Length of Service

The Chairperson serves 3-year terms and may be re-appointed.

(3) Responsibilities:

(a) Establishing the meeting calendar;
(b) Conducting IRB meetings;
(c) Directing the IRB Coordinators to ensure operation of the IRB within all applicable regulatory requirements;
(d) Reviewing and signing IRB minutes that summarize the actions and reasons for these actions of each presented protocol;
(e) Reviewing and acting on requests for exemption from IRB review;
(f) Reviewing requests for expedited review and, if the expedited process is appropriate, either approving the study on behalf of the IRB, or assigning a reviewer who will advise the Chair, so that the Chair can then act on the request on behalf of the IRB. Requests that do not meet the criteria for expedited review will be considered by a fully convened IRB.
(g) Reviewing or assigning review of adverse event reports;
(h) The IRB Chairperson works with IRB members, institutional officials, and investigators to ensure that the rights and welfare of research subjects are adequately protected;
(i) Signing the final IRB approval paperwork, unless the Alternate Chair is presiding, for protocols or actions approved by the IRB;
(j) Reporting to the R&D Committee about IRB activities; recommending R&D approval of IRB actions;
(k) Reviewing all questions, concerns, complaints, and allegations of non-compliance with human research institutional policies that have been brought forward by the Research Assurance & Compliance Coordinator;
(m) Providing an initial orientation to IRB members to their committee activities and appropriate continuing education related to the IRB.(n) Forwarding any requests received for consultation received from investigators, research staff, clinicians, etc. to the IRB Coordinators for a documented response to the individual's questions. It is not the policy of the Portland VA Medical Center IRB to provide curbside consults to individual investigators and medical staff.

b. **IRB Members (38CFR16.107)**

The membership is selected to assure: appropriate diversity; based on representation by multiple professions; diverse cultural backgrounds; both genders; knowledge and experience with vulnerable subjects; inclusion of both scientific and non-scientific members; and sensitivity to community attitudes to promote respect for it's advice and counsel in safeguarding the rights and welfare of human subjects.

(1) **IRB Requirements**:

In addition to the diversity of membership, each IRB will have at least:

(a) Five members;
(b) One member whose primary area of interest is scientific, e.g. a scientific research principal investigator;
(c) At least one member whose primary area of interest is in a non-scientific area;
(d) At least one member who is not affiliated with the VA or who is part of the immediate family of a person who is affiliated with the VA;
An **affiliated member** is one who works at the VA Medical Center, is married to someone who works at the VA Medical Center or works for a company that contracts with the VA Medical Center.
(e) Members from more than one profession;
(f) One lay member who serves as the community representative;
(g) One member from the Research & Development Committee; and
(h) A member of the IRB may fill multiple membership position requirements for the IRB.

(2) **Appointment:** IRB members are nominated by the ACOS/R&D, voted on by the R&D Committee and formally appointed by the Medical Center Director.

(3) **Length of Service:** Members serve at least 3-year staggered terms. Regular attendance at IRB meetings is expected, and a member may be removed from the IRB on the basis of repeated unexcused absences or non-attention to the functions and responsibilities of the IRB.

(4) **Responsibilities:**

(a) Members are responsible for ensuring that the rights and welfare of research subjects are protected.
(b) Learning about, and remaining current on, ethical, legal and regulatory issues related to IRB business.
(c) Completion of appropriate IRB reviewer forms.
(d) Reviewing and assuring the Chair that all minor changes requested by the IRB were made for research projects contingently approved by the IRB.
(e) Maintaining the integrity of the IRB review process. In particular, members must avoid discussing IRB protocols with investigators outside of a convened IRB meeting in a manner that would suggest possible IRB determinations.
(f) Members vote to approve as presented, approve after the minor modifications have been made and verified by the Primary Reviewer (contingent approval), defer (table) for major modifications, or disapprove research submitted to the IRB.
(g) Members are expected to serve as primary reviewers when assigned, generally within their areas of expertise, and serve as general reviewers on all research discussed at convened meetings.
(h) Members are also expected to conduct expedited reviews on behalf of the IRB when so designated by the IRB Chairperson.
(i) Members may be asked to participate in other subcommittees, audits, and education, as long as there is no conflict of interest with the IRB responsibilities.
(j) In addition to completing the education requirements set forth by the IRB Chair, also successfully completing the education requirement in the protection of human research participants.
(k) All members of the IRB must avoid conflicts of interest (38 CFR 16.107(e)) or the appearance of conflict of interest in relation to any submission, including the IRQ, scientific protocol, or informed consent forms reviewed by the IRB. They must

determine whether or not any conflicts of interest exist between the chair or other members of the IRB and the research project to be reviewed, prior to review of the research project. This includes both initial and continuing review. No individual who is in a position of conflict of interest with a study will be permitted to be either a primary or continuing reviewer of the study. During the convened meeting, if such conflicts of interest exist, the conflicted member will leave the room during the discussion and vote. The chair or alternate chair, if a conflict of interest exists, may invite the conflicted member into the room to answer questions the members may have during the review process. However, the member must again leave the room for the remainder of the discussion and vote on the research project. The member in conflict is instructed not to discuss the vote or who voted in any particular direction with any members of the IRB, but rather see the discussion and vote in the IRB meeting minutes. The minutes will also note when a conflicted member was absent for the vote. This is referred to as "recused." For further information regarding conflict of interest, please see the Human Research Protection Program: Policy & Procedure No. 5, "Conflict of Interest in Human Research," located in Appendix M.

(l) Forwarding any requests for consultation from investigators, research staff and clinicians, etc. received to the IRB Coordinators for a documented response to the individual's questions. It is not the policy of the Portland VA Medical Center IRB to provide curbside consults to individual investigators and medical staff.

The current composition of the IRB in terms of members by name, degrees held, voting and alternate status and representative capacity is in Appendix D. In addition, the membership is summarized on the full board meeting minutes of the IRB.

c. **Alternate IRB Members**. Alternate members may be nominated by the ACOS/R&D, voted on by the R&D Committee and appointed by the Medical Center Director. These alternates are nominated with the same criteria of selection as primary IRB members. These alternates replace regular IRB members who are, on occasion, unable to attend convened meetings of the IRB. All alternates are identified on the IRB Alternate rosters in Appendix D and are identified as to whom they may substitute at convened meetings. IRB minutes will record when alternate members act in the absence of primary members. All alternate members will receive the same reviewer information as primary IRB members when they will be attending meetings for the absent member.

d. **Non-Voting and Ad Hoc Members (M-3, Part 1, Chapter 9.08(f))**. The IRB does not include "non-voting" members, other than ex-officio members, who are appointed due to their position at the PVAMC and/or ad hoc members, who are invited by the R&D Committee and/or IRB because of their competence in a certain area to assist in the review of issues which require expertise beyond or in addition to that available to the IRB. These ex-officio and ad hoc members may not vote with the IRB. These members are not nominated and appointed by the Medical Center Director. The Administrative Officer/Research & Development serves as an ex-officio member of the IRB.

e. **Compensation for IRB Service.** No IRB members are compensated for serving on the IRB, but may receive reimbursement for travel costs.

f. **Use of Consultants (38 CFR 16.107(f)).** The IRB is authorized to obtain services of ad hoc reviewers when additional expertise is required.

g. **Training of IRB Chair and Members (ORB May 8, 2000, and March 14, 2001, Memoranda)**
Note: this specific section of the PVAMC IRB SOP was edited and approved by the IRB on March 12, 2003.
As a condition of the FWA, IRB members are provided education about human research protection.

The IRB Chair and Members are responsible for meeting the educational requirements as set forth in the PVAMC Human Research Protection Program: Policy & Procedure No. 4, "Education for the Protection of Human Research Participants in the Research & Development Service," and for any other education as required by the IRB Chair. The HRPP: Policy & Procedure No. 4 is located in Appendix L.

All IRB members receive a copy of the Portland VA Medical Center Institutional Review Board Standard Operating Procedures developed by Dennis J. Mazur, M.D., Ph.D., Sola Whitehead, C.I.P., and Angie Lacey, Research Assurance & Compliance Coordinator prior to their first meeting with the IRB.

This IRB SOP binder includes the IRB SOP and its appendices, in addition to a complete section of pertinent regulations. In addition, the IRB Chair presents contemporary topics facing IRBs in the United States in a didactic and question and answer session that can occur quarterly at the IRB meeting.

It is the responsibility of the Chairperson of the IRB and the Research Service to provide members with an initial orientation to their committee activities and appropriate continuing education related to the IRB.

Each new IRB member's training, as of October 2002, consists of the following:

(1) Members are given a copy the IRB SOP Binder which contains all relevant educational materials.
(2) The IRB Chair meets with the new IRB member either one on one or in cases of more than one new IRB member receiving training, as a group. The IRB Chair discusses with the members the parameters of IRB decision-making and answers any questions the new IRB member(s) may have regarding his/her/their responsibilities as an IRB member(s) and the functioning of the IRB.
(3) The IRB Chair also presents an educational course where he discusses the development of the IRB within the United States and focuses on contemporary issues facing the Portland VAMC IRB in its review of protocols in light of contemporary issues in research related to study participants.
(4) The IRB Chair presents contemporary topics facing IRBs in the United States in a didactic and question and answer session that can occur quarterly at the IRB meeting.
(5) Each new member is assigned studies to review based on the unique expertise of the member, i.e. strengths, education, and experience levels.

5. **IRB Recordkeeping and Required Documentation (38CFR16.115).**

a. **Record Retention (38 CFR 16.115(b)).** The IRB shall keep records for at least 3 years after consideration for disapproved proposals and 3 years after the conclusion of research for approved proposals. All IRB records collected over the course of the protocol will be maintained by the IRB

Coordinators in the PVAMC Research Service space. If a study does not receive funding and the PI decides not to conduct the research without funding, the records will also be kept for three years.

b. **Access to IRB Records (38 CFR 16.115(b)).** IRB records are the property and the responsibility of the PVAMC Research Service office. These records are stored by the Research Service at the PVAMC either in the Research Service office, or in storage areas in locked file cabinets behind magnetic security doors in order to maintain the privacy and confidentiality of research subjects' information. Electronic records are kept on a password-protected computer maintained by the Research Service staff as part of their official employment duties.

IRB records are accessible to the Research Service staff, Chairperson and IRB members. Research investigators shall be provided reasonable access to files related to their research. Other authorized individuals, such as accrediting officials and officials of Federal and state regulatory agencies, including the: Office of Research Oversight (ORO) (aka. Office of Research Compliance and Assurance (ORCA), the Office for Human Research Protections (OHRP), and the Food and Drug Administration (FDA), will have access to IRB records for inspection and copying upon determination of appropriateness and necessity at reasonable times and in a reasonable manner. Appropriate accreditation bodies shall be provided access and may recommend additional procedures for maintaining security of IRB records.

A log of such individuals who do access the IRB records, excluding the IRB members and Research Service staff, is maintained by the IRB Coordinators and/or Research Service staff.

c. **IRB Records.** The IRB records include:

(1) **Written operating procedures**
(2) **Documentation of convened IRB meeting minutes**
(3) **IRB Membership Information**
(4) **Training Records**
(5) **Research project files**
Research project records are in organized files and contain all documentation associated with the research project. This includes the research proposal reviewed, records of continuing review activities, copies of all correspondence between the IRB and the investigator, as well as scientific evaluations, sample consent documents, progress reports and any reports of injuries to subjects, when applicable.
(6) **Federalwide Assurance (FWA)**

d. **IRB Membership Roster**

The IRB maintains the current IRB membership rosters and reports any changes to the OHRP with a copy to the Office of Research Oversight (ORO) (aka. Office of Research Compliance & Assurance (ORCA)). The IRB Coordinators are responsible for maintaining updated IRB rosters. The rosters include name, degrees held, voting and alternate status and representative capacity (i.e., staff member, lay person, etc.). The IRB membership roster are included in Appendix D. The IRB Member Information binder contains copies of the IRB members' CVs and appointment letters.

e. **Education Records.** The Research Service office shall maintain accurate records of research investigators, research staff, IRB members, and IRB staff who have fulfilled the PVAMC HRPP education requirements.

Please see the Human Research Protection Program: Policy and Procedure No. 4, Education for the Protection of Human Research Participants in the Research & Development Service, for a detailed description of the education requirements and the individuals required to complete the requirements. The Research Assurance & Compliance Coordinator is responsible for maintaining and monitoring the tracking database for all individuals completing the HRPP education requirements as described in this policy.

The IRB Coordinators are responsible for maintaining any additional education and training records of IRB members.

f. **Written Standard Operating Procedures and Guidelines (38 CFR 16.103(b) (4, 5) and 108(a), 115(a)(6)).** IRB members are provided with a copy of the standard operating procedures both electronically and hard copy at the time they join the IRB, and each time the SOP is updated.

The IRB Chairperson, IRB Coordinators, and Research Assurance & Compliance Coordinator work together to write and maintain the IRB SOP. The SOP will be reviewed and modified as needed to reflect updated and applicable regulations, policies, and institutional procedures.

g. **IRB Correspondence (38 CFR 16.115(a)(4)).** Accurate records are maintained of all communications to and from the IRB. IRB correspondence is signed by an IRB Coordinator present at the meeting or at such time as the text of such correspondence is confirmed with the IRB Chair. Copies of all correspondence are filed in the appropriate investigator research project file, which are located in the PVAMC Research Service office or designated storage area (Section III 5 (b)).

Upon initial review, results of that review are sent to the principal investigator or designated study coordinator within a reasonable time frame upon the resolution of items reviewed outside of a convened meeting.

In cases in which a project being performed at the PVAMC has multiple investigators, correspondence will be sent to the investigator primarily in charge of the study or to the study coordinator designated to receive such correspondence, as noted on the IRQ or PPQ. If the study coordinator is designated to receive such correspondence as noted on the IRQ or PPQ, the study coordinator will be responsible for communicating the results of the review to the principal investigators. The principal investigator is ultimately responsible for the research project and assuring that the research project and staff comply with IRB requirements. In cases where communication is electronic, upon resolution of the topic of the communication, a hard copy will be generated and filed with the project file by the IRB Coordinator and/or staff.

h. **IRB Research Project Files.** The IRB shall maintain a separate file for each research project. Protocols are assigned a unique number from the MIRB for tracking and administration purposes. A separate unique VA grant number is also assigned, and is associated with each protocol. This VA grant number serves as another method of identifying the grant. The IRB application shall include the documents in Appendix C, as applicable to the protocol.

i. **Research Tracking System.** The IRB uses a reliable computerized tracking system, the MIRB computer program, which is maintained by the IRB Coordinators and Research Service staff. MIRB stores information regarding which documents have been received, when they were reviewed, and the results of that review.

Additionally, MIRB tracks changes that are needed, when those changes were received and approved, and the date of continuing review for research projects reviewed by the IRB.

IRB membership is tracked, and IRB correspondence and minutes are generated by MIRB.

j. **Items Requiring IRB Review**
If there is any element of research in any activity involving human subjects and/or human data and/or human biological specimens, the activity must undergo Institutional Review Board (IRB) review and approval before the research project may begin. The IRB and R&D Committee will then determine whether or not the research activity is exempt from the human subjects regulations and purview of the IRB. Questions regarding whether or not IRB review and approval is required, must be directed in writing to the IRB Coordinators. Requests for determination submitted to the IRB Coordinators should include a detailed explanation of the research question and how the research will be conducted. The IRB Coordinators will forward written requests to the IRB when necessary.

k. **Documentation of Exemptions from IRB Oversight/Review.**
Investigators shall submit a written request to the IRB for an exemption from IRB review. This should be completed through the "Certification of Exemption Form." The IRB serves as the R&D Committee's designee in the review of exempt status based on categories stipulated at 38CFR16.101 to the IRB. The IRB is to communicate that status in writing to the investigator. The IRB Chair will recommend approval of the exempt status to the R&D Committee who will review and make a final determination (M-3, Part1, Chapter 9.06). This may be done via expedited procedures. Any individual involved in making the determination of exempt status of a proposed research project cannot be involved in the proposed research.

Documentation regarding the rationale for the exemption, the category and circumstances will be completed by the IRB Chair or the Chair's qualified designee and will be maintained in Research Service records. The IRB will be notified of the review and decision at the next convened IRB meeting and it will be documented in the meeting minutes.

Categories of exempt research are stipulated in VA regulations at 38 CFR 16.101(b)(1-6) and the Common Rule as follows:

(1) Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as: (a) research on regular and special education instructional strategies, or (b) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

(2) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless: (a) Information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and (b) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.

(3) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph (2)(b) of this section, if: (a) The human subjects are elected or appointed public officials or candidates for public office; or (b) federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

(4) Research, involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

(5) Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which are designed to study, evaluate, or otherwise examine: (a) Public benefit or service programs; (b) procedures for obtaining benefits or services under those programs; (c) possible changes in or alternatives to those programs or procedures; or (d) possible changes in methods or levels of payment for benefits or services under those programs.

(6) Taste and food quality evaluation and consumer acceptance studies, (a) if wholesome foods without additives are consumed or (b) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration (FDA) or approved by the Environmental Protection Agency (EPA) or the Food Safety and Inspection Service of the U.S. Department of Agriculture. This also applies to FDA regulated research.

Note: These exemptions are not available for all kinds of research (38 CFR 16.101(i)). There are restrictions based on the populations to be studied: research involving prisoners or focused primarily on pregnant women, human in vitro fertilization or fetuses may be exempted, and research that falls in category (2) may not be exempted when children are subjects if the investigator will interact with the child, as in survey or interview research.

l. **Documentation of Exceptions from Informed Consent for Emergency Use of a Test Article (21 CFR 50.23).** FDA regulations at 21 CFR 50.23 permit the use of a test article without the informed consent of the subject (or the subject's legally authorized representative) when the clinical investigator and a physician not otherwise involved in the research certify in writing all of the following:

(1) The subject is confronted by a life-threatening situation necessitating the use of the test article;
(2) Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject and there is a medical emergency or urgency;
(3) Time is not sufficient to obtain consent from the subject's legal representative and there is a medical emergency or urgency; and

(4) No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life and there is a medical emergency or urgency.

After Use Procedures for Waiver of Informed Consent Under Compassionate Use or on an Emergency Basis:

If time is not sufficient to obtain an independent physician's determination that the four conditions above apply, the clinical investigator should make the determination and within 5 working days after the use of the article have the determination reviewed and evaluated in writing by an independent physician. Additionally, the IRB must be notified within 5 working days after use of the test article. The IRB Coordinator is responsible for maintaining this documentation in IRB records.

m. **Documentation of Expedited Reviews (38 CFR 16.110(b); 63FR 60364-60367, November 9, 1998).** Upon request by a principal investigator for expedited review, the Chairperson or Alternate Chair of the IRB will review the material to assess the appropriateness of the request. In cases where an expedited review is appropriate, the Chairperson or designated IRB member will conduct such review. The review will be documented in the research project file and the next meeting minutes of the IRB. Expedited review will only be used in cases which meet all expedited review requirements.

n. **Documentation of Convened IRB Meetings – Minutes (38 CFR 16.115(a)(2)).** IRB minutes are completed by the IRB Coordinators in MIRB. Minutes shall include:

(1) Attendance by name at the meeting;
(2) Approval of prior meeting minutes;
(3) Actions taken by the IRB on the following: initial or continuing review of research, specific measures taken to protect vulnerable populations, review of protocol or informed consent modifications or amendments, unanticipated problems involving risks to subjects or others, adverse event reports, reports from sponsors, cooperative groups, or Data Safety Monitoring Boards (DSMB), reports of continuing non-compliance with the regulations by investigators and other staff or IRB determinations, waiver or alteration of elements of informed consent and justification, suspensions or terminations of research, and other actions as appropriate;
(4) Votes on these actions, including the number of members voting. These are categorized according to the following: "for, against, abstain, recused, and excused."
Recused is used when a conflict of interest has been identified for a member of the IRB. The member is not allowed to participate in the deliberations or vote on the research project.
Excused is used when a member of the IRB was out of the room for the vote, i.e. restroom, emergency, etc.
(5) The basis for requiring changes in or disapproving research;
(6) Summary of controverted issues and their resolutions;
(7) A list of research approved since the last meeting utilizing expedited review procedures and the specific citation for the category of expedited review of the individual protocol.

(8) The names of persons who excused themselves during the review of a protocol; and

(9) Determination of the frequency of continuing review of each research project based upon the degree of risk, as determined by the IRB.

After being signed by the IRB Chair, a copy of the IRB meeting minutes will be forwarded to the R&D Coordinator. These minutes will be reviewed by the R&D Committee at the next convened R&D Committee meeting.

o. **Attendance at IRB Meetings.** IRB minutes shall list attendance according to the following:
Note: (2) – (6) will be documented as appropriate.

(1) Names of members present;

(2) Names of absent/excused members;
Excused is used when a member has alerted an IRB Coordinator in advance of the meeting that he/she will be absent.
Absent is used when a member has not alerted an IRB Coordinator in advance of the meeting that he/she will be absent.

(3) Names of alternates attending in lieu of specified (named) absent members. Alternates may substitute for specific absent members only as designated on the official IRB membership roster;

(4) Names of ad hoc reviewers present;

(5) Name of investigators present; and

(6) Names of guests present.

p. **Quorum Requirements and Voting at IRB Meetings (M-3, Part 1, Chapter 9.09.e).** The IRB will not conduct business without a quorum present. IRB meeting minutes reflect: the circumstances in which members with conflicts of interest did not participate in the deliberations or voting, noted as "recused." In addition, if a non-scientific member of the IRB is absent during the meeting, i.e. if the non-scientific member is absent or excused, this is indicated in the meeting minutes.

(1) A majority of the IRB members (or their designated alternates), including at least one member whose primary concerns are in nonscientific areas, must be present to conduct a convened meeting. In order for research to be approved, it must receive the approval of a majority of those members present at the meeting.

(2) Members may be present in person or audio (telephone) or audio-visual teleconference. Members present via teleconference shall be noted as such in the meeting minutes, which shall also indicate that the members received all pertinent information prior to the meeting and were able to actively and equally participate in all discussions.

(3) IRB minutes shall include documentation of quorum and votes for each IRB action and determination by recording votes number voting: for ( ); against ( ); abstaining ( ); recused ( ); excused ( ).

(4) Members absenting themselves due to conflicts of interest will be documented as "recused" during the vote. The member may not be counted toward quorum requirements (i.e., may not be counted among those voting or abstaining) or be counted as among the majority of members necessary to constitute a quorum.

(5) The following individuals will not be considered as part of the quorum and will not vote with the IRB:
(a) An individual who is not listed on the official IRB membership roster;
(b) Any ex-officio member of the IRB; and
(c) Ad Hoc reviewers.
(6) At least one non-scientist must always be present for a vote to be taken.
(7) When a member and his/her alternate both attend a meeting, only one can vote.

q. **Actions Taken by the Convened IRB (38 CFR 16.109; 115).** The minutes shall include all actions taken by the convened IRB and the votes underlying those actions.

IRB actions for review of research include the following:

(1) **Approved** (Approved with no changes or no additional changes). The research may proceed. **Note:** if it is the **initial** review of the research project, R&D Committee approval is required **prior** to study initiation.
(2) **Contingent Approval (Approvable with minor changes)** to be reviewed by a designated IRB member. Such minor changes must be clearly delineated by the IRB so the investigator may simply comply with the IRB's stipulations. The research may proceed after the required changes are verified by the designated reviewer and approved by the IRB chair. R&D Committee approval is also required prior to study initiation.
(3) **Tabled (deferred)** pending receipt of additional substantive information or substantive changes. The IRB determines that it lacks sufficient information about the research to proceed with its review or that the changes are so numerous as to require re-review by the full board. This category is referred to as "Tabled" in the IRB correspondence and minutes. The research may not proceed until the convened IRB has approved a revised application at a convened meeting.
(4) **Disapproved**. The IRB has determined that the research cannot be conducted at the facility or by employees or agents of the facility.

IRB actions, during the review of adverse events occurring during the period for which the research project is authorized and also at the time of continuing review, determine whether or not the **risks to subjects** have changed and decide whether or not the research:

(1) May continue;
(2) May continue with modifications;
(3) Must be suspended; or
(4) Must be terminated.

r. **The Basis for Requiring Changes in or Disapproving Research (38 CFR 16.109(d)).** The minutes of IRB meetings shall include the basis for requiring changes in or disapproving research.

Investigators or their designated coordinators as designated on the IRQ or PPQ shall be notified in writing of the determination of the IRB, and any changes that are required by the IRB. These will be sent electronically via e-mail, and a signed hard copy of the correspondence will be mailed to the investigator for their files. Responses to the IRB should come from the investigator or a designated

study coordinator, and may be communicated electronically or by hard copy. Prior to final approval, the changes the IRB has requested must be reviewed and confirmed by either the designated IRB reviewer or convened IRB, whichever the IRB has designated. Upon final review and approval by the IRB, VA Form 10-1223 will be completed and signed by the IRB Chairperson.

s. **Summary of Controverted Issues at Convened Meetings (38 CFR 16.115(a)(2)).** The minutes of IRB meetings shall include a written summary of the discussion of controverted issues and their resolution.

t. **IRB Findings and Determinations where Documentation is Required by Regulation (OHRP and FDA Guidance).** The IRB members shall use the appropriate "IRB Primary Reviewer Form" in reviewing protocols at the time of initial and continuing review. A copy of the checklists are included in Appendix E. IRB determinations of the IRB, regarding the following items are documented in the IRB minutes.

(1) The level of risk of the research.

(2) The approval period for the research, including identification of research that warrants review more often than (at least) annually.

(3) Justification for waiver or alteration of informed consent, addressing each of the four (4) criteria at 38 CFR 16.116(d). (Note: This cannot be done if an FDA test article is involved.)

(4) Justification for waiver of the requirement for written documentation of informed consent in accordance with the criteria at 38 CFR 16.117(c).

(5) For DHHS-supported research, justification for approval of research involving pregnant women, human fetuses, and human in vitro fertilization, addressing each of the criteria specified under 45 CFR 46 Subpart B of the DHHS human subject regulations. **Note:** The PVAMC does not review or conduct research directly involving human fetuses or human in vitro fertilization.

(6) For DHHS-supported research, justification for approval of research involving prisoners, addressing each of the categories and criteria specified under 45 CFR 46 Subpart C of the DHHS human subject regulations. Generally, the IRB Coordinator is responsible for providing certification of the IRB's findings to OHRP. **Note:** The PVAMC does not review or conduct research with prisoners.

(7) For DHHS and VA supported and FDA regulated research, justification for approval of research involving children, addressing each of the categories and criteria specified under 45 CFR 46 Subpart D of the DHHS and FDA human subject regulations. VA policy specifies that a waiver for research involving children must be obtained from the Chief Research and Development Officer (VHA Directive 2001-028, April 27, 2001). Generally the IRB Coordinator is responsible for providing notification to OHRP of the IRB's findings concerning research requiring review by a panel of experts convened in accordance with Subpart D. For FDA regulated research documentation of the IRB findings is required. Notification shall go to the Commissioner of the FDA.

(8) Special protections warranted in specific research projects for groups of subjects who are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or

educationally disadvantaged persons, regardless of source of support for the research.

(9) Justification for approval of research planned for an emergency setting, with specific reference to the criteria specified under the special 45 CFR 46.101(i) DHHS waiver or the FDA exception at 21 CFR 50.24. (Note: VA researchers cannot use these provisions. Please refer to Policy Clarification and e-mail dated 10/04/2002, regarding No Planned Emergency Research in Appendix R.)

6. Types of IRB Review Determinations. Unless determined to be exempt, all human subject research conducted at the PVAMC facility or by PVAMC employees or agents or otherwise under VA auspices must be reviewed and approved by the IRB and by the R&D Committee prior to initiation. No human subject research may be initiated or continued at the facility or by employees or agents without the appropriate approvals of both the IRB and R&D Committee. Regardless of the type of review (approved as exempt, expedited or reviewed at a convened meeting), the investigator is notified in writing of the IRB's and R&D Committee's determinations.

a. **Review by the Convened IRB (38 CFR 16.108(b)).** The IRB will conduct initial and continuing reviews of all non-exempt research at convened meetings at which a quorum of the members is present, including a member whose primary interest is non-scientific, unless the research falls into one or more categories appropriate for expedited review.

The current IRB meeting schedules are listed in Appendix B as well as in the Research Service office. Principal Investigators must submit information to the Research Service office by the 20th of the month for review at the following month's scheduled IRB meeting. The IRB review materials and all applicable primary review materials are dispersed to the IRB members approximately one week prior to the next convened meeting to allow for sufficient review in order to discuss the protocol adequately and determine the appropriate action during the convened meeting. IRB review materials include all of the materials as described in Section 6(b). Once a research project is reviewed by either IRB #1 or #2, the research project will stay with the same IRB for the life of the protocol.

(1) **Initial Review by the Convened IRB (38 CFR 16.103(b)(4) and 21 CFR 56.108-109).** The IRB must conduct an initial review of all proposed research projects involving human subjects, unless it is determined to be exempt from IRB review or has previously undergone appropriate expedited review procedures. The proposed research project must be approved by the IRB and R&D Committee prior to initiation. During the initial review, the IRB will determine the period and time for continuing review, as appropriate to the degree of risk of the research project. Members will use the IRB Primary Reviewer Form as noted in Appendix E to assist in determining risk level and ensuring that the information provided meets appropriate guidelines.

(2) **Review of Amendments, Changes and Deviations to IRB Approved Research Procedures and Consent Forms**
The IRB must conduct a review of all proposed modifications to research projects, including modifications to informed consent forms, and approve them prior to the implementation of the proposed changes. The proposed modifications should be submitted to the Research Service office with the

"Project Revision/Amendment Form (PR/AF- Appendix C)." These modifications will be reviewed by the Primary Reviewer System, presented to and voted on at the full IRB at the convened meeting. The Primary Reviewer will receive the "PR/AF," most current IRB approved consent form, documents that include the proposed changes and the current IRB approved document that is up for review of proposed changes, if one exists.

(3) **Review of Investigator Non-Compliance**
The IRB will address and review any questions, concerns, complaints and allegations of non-compliance with human research institutional policies and federal regulations that are brought to the IRB. The IRB will determine the validity of all complaints and make a recommendation for corrective action. The minutes of the IRB meeting will record the discussion, deliberation and final recommendation to the R&D Committee. Please see Human Research Protection Program: Policy & Procedure No. 3, "Complaints and Allegations of Non-compliance in Human Research," in Appendix K for more details.

(4) **Continuing Review by the Convened IRB (38 CFR 16.103(b)(4)and 109(e)).** The IRB will conduct substantive and meaningful continuing review of research at intervals appropriate to the degree of risk, but not less than once per year. The IRB approval period for research may not extend more than 365 days after the convened IRB meeting at which the research was last reviewed and approved, or approved with minor contingencies not requiring additional full IRB review. This information will include all applicable IRB submission materials as noted in Appendix C.

(a) **During the continuing review, the IRB takes the following into consideration:**

i. changes to the research;
ii. adverse event reports;
iii. safety reports, including IND, IDE and MedWatch;
iv. protocol violations and/or deviations; and
v. investigator non-compliance, including non-compliance with IRB requirements for frequency of periodic continuing review.

(b) The investigator will receive materials to submit for the continuing review approximately sixty days before the current approval for the research project expires. Investigators are asked to submit the materials in time for the next month's meeting, allowing for review approximately 30 days before the protocol's expiration date. If the material is not submitted in a timely manner and it is not possible to get the materials to the IRB meeting, the study may be suspended.

(c) Studies that meet expedited review criteria at the time of initial review, may meet expedited review criteria for continuing review, and this determination will be made by the IRB Chairperson.

b. **Use of Primary Reviewers with Convened IRB Reviews.** The IRB Coordinators of the Research Service will make a preliminary review of the IRB application at the time of receipt and assign at least two primary reviewers to review the protocol for the next IRB meeting, according to consistency with the protocol content and reviewer knowledge and expertise. The primary reviewers for initial review, and for continuing review, are considered the lead reviewers on the IRB for the research project assigned to them. They are responsible for (1) being thoroughly versed in all details of the research; (2) conducting an in-depth review of the research (3) completing the applicable IRB reviewer forms contained in Appendix E; and (4) leading the discussion of the research at the convened meeting, voicing any concerns that arose during their review and changes that may be required.

During the initial review of a research project, all IRB members receive a copy of the Initial Review Questionnaire, the abstract, the proposed consent form and any proposed advertising materials for a research project proposal. In addition to the above stated material, the primary reviewers for each research project receive a research project's complete protocol, the clinical investigator's brochure(s) and any other applicable material in order to have the complete application to ensure a thorough initial review of the research project proposal. This may include: subject information, subject surveys or questionnaires, application for merit reviews or grant applications where applicable.

During the continuing review of a research project, all IRB members shall be provided with a copy of the "Continuing Protocol Review," which identifies the number of subjects accrued and a summary of adverse events, unanticipated problems, any withdrawal of study subjects, and complaints about the research; the updated research project abstract; and the most current IRB approved informed consent form. In addition to the above stated material, the primary reviewers for each research project also receive the "Continuing Review Submission Form" and the complete protocol to ensure a thorough continuing review of the research project.

IRB members will receive these materials approximately one week prior to the scheduled convened meeting. During the initial review of a research project, the entire IRB file is given to the primary IRB reviewers prior to the convened meeting. During the continuing review of a research project, the entire IRB file is available to the primary reviewer prior to and during the convened meeting. All IRB members shall be afforded full opportunity to discuss each research proposal during the convened meeting.

c. **Outcomes of IRB Review (38 CFR 16.109(d) and 115).** The IRB shall notify investigators and the R&D Committee in writing of its determinations as determined in Section 5(p) and 5(q). Copies of all correspondence between the IRB and the investigator will be filed in the appropriate research project file.

d. **Review of Proposed Foreign Research**
The Portland VAMC IRB recognizes the crucial problems of oversight in the conduct of scientific research in foreign countries and will consider such research in the most rare of circumstances.

The Portland VAMC IRB will review all requests from principal investigators related to foreign research. However, the IRB also recognizes the problems that exist with oversight of such foreign research and the IRB recognizes that such research requests will be rare and most typically under the oversight of the National Institute of Health (NIH) or other federal regulatory agency. Even in these

rare cases where research may be conducted in a foreign country, the principal investigator will be required to demonstrate approval of a federal agency for the research study, and demonstrate local foreign approval.

e. **Expedited Review of Research (38 CFR 16.110).** The IRB Chairs will make a determination on whether or not a protocol may be reviewed using expedited procedures. The individual(s) making this determination cannot be involved in the proposed research. This decision is based on either or both of the following:

(1) The research constitutes a minor change in previously approved research during the period of 1 year or less for which approval is authorized; or

(2) The research is not greater than minimal risk and falls within the categories on the November 9, 1998, DHHS-FDA list of research eligible for expedited IRB review published in the Federal Register, 63 FR 60364-60367.

The Chairs may review the expedited review request and research project or the Chairs may designate a member to complete the review of the request and research project. The designee to review the request and research project must be a voting member of the IRB and have qualifications, experience and knowledge in the content of the protocol to be reviewed, as well as be knowledgeable of the requirements to approve research expeditiously. The reviewer may exercise the authority of the IRB, but may not disapprove the research. The research may only be disapproved after non-expedited review by the convened IRB.

The fully convened IRB will be notified of all research approved under expedited procedures in the IRB meeting agenda and minutes. A copy of the expedited request and approval, or appropriate items, will be included in the IRB agenda packets for review by the convened IRB. All correspondence resulting from an expedited review will note such and be filed with the Research Services's research project file kept in the appropriate Research Service space. Documentation for expedited reviews maintained in IRB records shall include the category and circumstances that justify using expedited procedures.

f. **Expedited Review of Minor Changes in Previously Approved Research (38 CFR 16.110(b)).** VA regulations at 38 CFR 16.110, the Common Rule, and FDA regulations permit the IRB Chair or his/her designee(s) to review research through an expedited procedure if minor changes are in previously approved research during the period (of one year or less) for which the approval is authorized. The expedited review and reviewer requirements are such as stated in Section (e) above. The individuals making this determination cannot be involved in the proposed research.

A **minor change** is one which, in the judgment of the IRB Chairperson or reviewer, makes no substantial alteration in (1) the level of risks to subjects; (2) the research design or methodology; (3) the number of subjects enrolled in the research; (4) the qualifications of the research team; (5) the facilities available to support safe conduct of the research; or (6) any other factor which would warrant review of the proposed changes by the convened IRB.

Investigators must report to the IRB any proposed changes in IRB-approved research, including proposed changes in informed consent documents. The investigator may request an expedited review of minor changes in previously approved research. However, no changes may be initiated without

prior approval of the IRB, except where necessary to eliminate apparent immediate hazards to subjects.

The fully convened IRB will be notified of all minor changes in research approved under expedited procedures in the IRB meeting agenda and minutes. A copy of the expedited request and approval, or appropriate items, will be included in the IRB agenda packets for review by the convened IRB. All correspondence resulting from an expedited review will note such and be filed with the Research Services's research project file kept in the appropriate Research Service space.. Documentation for expedited reviews maintained in IRB records shall include the category and circumstances that justify using expedited procedures.

g. **Expedited Initial and Continuing Review: Permitted Categories.** Expedited procedures are used for initial and continuing review of research that is no greater than minimal risk **and** falls within the categories published in the November 9, 1998, Federal Register 63 FR 60364-60367. The categories for research projects eligible for initial and continuing review are stated below. Even though a proposed research project may fall into the following categories, expedited review will be considered but is not guaranteed.

Applicability:

(1) Research activities that (1) present no more than minimal risk to human subjects, and (2) involve only procedures listed in one or more of the following categories, may be reviewed by the IRB through the expedited review procedure authorized by 45 CFR 46.110 and 21 CFR 56.110. The activities listed should not be deemed to be of minimal risk simply because they are included on this list. Inclusion on this list merely means that the activity is eligible for review through the expedited review procedure when the specific circumstances of the proposed research involve no more than minimal risk to human subjects.

(2) The categories in this list apply regardless of the age of subjects, except as noted.

(3) The expedited review procedure may not be used where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subject's financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.

(4) The expedited review procedure may not be used for classified research involving human subjects.

(5) The standard requirements for informed consent (or its waiver, alteration, or exception) apply regardless of the type of review--expedited or convened--utilized by the IRB.

All of the below categories pertain to initial and continuing review of research projects. These categories include:

(1) Clinical studies of drugs and medical devices only when condition (a) or (b) is met:

(a) Research on drugs for which an investigational new drug application (21 CFR 312) is not required. *(Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)*

(b) Research on medical devices for which (a) an investigational device exemption application (21 CFR 812) is not required; or (b) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

(2) Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:

(a) From healthy, non-pregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or

(b) From other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

(3) Prospective collection of biological specimens for research purposes by noninvasive means.

Examples: (a) hair and nail clippings in a non-disfiguring manner; (b) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction; (c) permanent teeth if routine patient care indicates a need for extraction; (d) excreta and external secretions (including sweat); (e) uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue; (f) placenta removed at delivery; (g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor; (h) supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques; (i) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings; (j) sputum collected after saline mist nebulization.

(4) Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.)

Examples: (a) physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy; (b) weighing or testing sensory acuity; (c) magnetic resonance imaging; (d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography; (e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

(5) Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes (such as medical treatment or diagnosis). *(Note: Some research in this category may be exempt from the DHHS regulations for the protection of human subjects at 45 CFR 46.101(b)(4). This listing refers only to research that is not exempt.)*

(6) Collection of data from voice, video, digital, or image recordings made for research purposes.

(7) Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. *(Note: Some research in this category may be exempt from the DHHS regulations for the protection of human subjects. 45 CFR 46.102(b)(2) and (b)(3). This listing refers only to research that is not exempt.)*

For **continuing reviews**, expedited reviews will only be considered in the following circumstances:

(8) Continuing review of research previously approved by the convened IRB as follows:

(a) Where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects; or

(b) Where no subjects have been enrolled and no additional risks have been identified; or

(c) Where the remaining research activities are limited to data analysis.

(9) Continuing review of research, which is **not** conducted under an investigational new drug application or investigational device exemption and where the categories in this Section 6 (g) for initial review (1)-(7) and continuing review (8) do not apply, but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

h. **Use of Subcommittees to Support IRB Activities.** The IRB Chairperson may appoint subcommittees on an ad hoc basis to perform non-review functions as needed, such as monitoring compliance with IRB regulations.

i. **Review of Reports of Unanticipated Problems involving risks to patients or Adverse Events (21 CFR 312.66). This also includes Safety Reports, IND, IDE and Medwatch Reports.**
All investigators conducting research as employees or agents in the PVAMC are required to notify the IRB promptly of any serious adverse events (SAEs) or unanticipated problems involving risks to subjects or others that occur in research conducted at the PVAMC or by PVAMC employees or agents, or under VA auspices. Principal Investigators are also required to report promptly to the IRB any adverse event (AE) that is reported to ORO, the FDA and/or the sponsor in accordance with FDA requirements.

Principal Investigators should complete an OHSU/PVAMC Adverse Event Report Form for all adverse events occurring for studies reviewed by the IRB. The form is available online at http://www.ohsu.edu/ra/rso/irb/aeform.doc. A copy of this form and the instructions are included in Appendix F. The form is one which tracks all adverse events which take place over the life of a protocol to allow tracking and enhanced monitoring of the adverse events. The Principal investigator must report any event that is unexpected, whether serious or not and all expected events that are serious (21 CFR 56.108(b)(1)). Serious events are those that are fatal, life-threatening, permanently disabling, or require inpatient hospitalization. Congenital anomalies, cancers, and overdoses are also considered serious (21 CFR 312.32(a)). **ALL** subject deaths must be reported for interventional studies, regardless of cause of death. The Principal Investigator must submit reports of all fatal or life-threatening events to the IRB within 24 hours of the event if it takes place at the PVAMC and submit within 24 hours of receiving notification for events at other sites. Additionally, he or she must submit all other reports within 10 days of the event if it occurs at the PVAMC, or within 10 days of notification for events at other sites.

The IRB Chairs will perform an initial review of all adverse events and unanticipated risks to a human subject either on site at the Portland VAMC or at a distance site. The Chair of the Portland VAMC IRB will review the notification in all of its detail and determine if immediate action is necessary. Immediate action may include calling a special meeting of the IRB to determine whether or not patients already enrolled in the study need to be informed of this new unexpected adverse outcome that has occurred, as well as to determine the proper change(s) to the informed consent form that will need to be made to inform patients of this heretofore unanticipated risk. In addition, at the special meeting of the IRB (if one is deemed necessary), it will be determined whether the study should be stopped until further information related to this unanticipated risk has been obtained or whether the study can continue with proper notification of enrolled patients and with proper changes to the existing informed consent form.

If immediate action is not needed, a primary reviewer will be assigned for review at the next IRB meeting, and results will be noted in the IRB minutes.

The IRB member that conducts the review of the adverse event evaluates and documents if the adverse event changes the risks to subjects for the study from the risks that are previously outlined in the current informed consent form. The IRB reviewer makes and documents a recommendation to the convened IRB, based on his/her review, whether or not the research may continue, may continue with modifications, must be suspended or must be terminated. If the research may continue with modifications, the IRB reviewer documents the modifications needed and whether or not all of the research subjects currently enrolled should be re-consented. This determination is discussed at a convened IRB meeting and the IRB then decides on the proposed action.

The IRB Chairs or ACOS/R&D shall provide prompt written notification to the PVAMC's R&D Committee and to relevant Federal agencies, including ORO, OHRP, and FDA (for FDA-regulated research) of any serious unanticipated problems involving risks to subjects or others, and of the resolution of those problems. The PVAMC will report information at the discretion of the R&D Committee, regarding the protection of human subjects in research consistent with the ORO (aka ORCA) Memorandum dated October 28, 2002, Attachment A. This includes: 1) findings of unanticipated problems involving risks to subjects or others. Adverse events that a) cause harm or pose risk of harm to research participants and for which an IRB takes substantive corrective action, i.e. substantive change(s) to the protocol and/or consent form, or restrictions, suspension or termination of study or investigator participation, or b) involve the death of healthy volunteers participating in research and 2) for cause suspensions and terminations (e.g. associated with unexpected harm).

j. **Review of Adverse Event or Safety Reports in Sponsored or Cooperative Group (Multi-center) Projects.** The IRB review of such reports is handled in the same manner as internal reports of unanticipated problems or adverse event as detailed in section III 6(i) above, unless otherwise approved by the IRB.

k. **Review of Data and Safety Monitoring Board (DSMB) Reports.** Data and Safety Monitoring Board Reports should follow the guidelines noted above for non-fatal events. The IRB Chairs will perform an initial review of all reports, and take action as needed, based on the nature of the report. If immediate action is not needed, a primary reviewer will be assigned for review at the next IRB meeting, and results will be noted in the IRB minutes.

When DSMBs are used, as indicated on the IRQ, the IRB may rely on a current statement from the DSMB indicating that it has reviewed study-wide AEs, interim findings, and any recent literature that may be relevant to the research, in lieu of requiring that this information be submitted directly to the IRB during the continuing review of the research project. Of course, the IRB must still receive and review reports of local, on-site unanticipated problems involving risks to subjects or others and any other information needed to ensure that its continuing review is substantive and meaningful.

l. **Review of Study Termination Reports**

The IRB reviews and acknowledges study termination reports upon receipt from the investigator. Investigators are to submit a notice of study termination to the IRB Coordinator upon completion of the research project. The notice should be submitted on the "Research Project Termination Report" form.

m. **Expiration of Approval Period (38 CFR 16.109(e)).**

Note: this specific section of the PVAMC IRB SOP was edited and approved by the IRB on March 12, 2003.

Per federal regulations, protocols may not be approved for more than 365 days from the time that the convened IRB voted on approval, or approval pending minor modifications, or the date of the expedited review process if expedited review was performed. The IRB will determine the length of the approval period at intervals appropriate to the degree of risk, and reserves the right to change the approval period at any time for any reason. Investigators are notified in writing of the approval date and the expiration date. Investigators will often first receive the information via e-mail, to be

followed by a signed hard copy of the correspondence noting such dates.

The regulations permit no grace period after approval expiration. Research that continues after the approval period expires is research conducted without IRB approval.

Consequently, the IRB shall automatically suspend the enrollment of new subjects in any ongoing research that does not receive IRB continuing review and approval prior to the end of the stipulated approval period. Previously enrolled subjects may continue their involvement in suspended research only where the IRB determines that continued involvement is in the best interest of the subjects.

If a research project is not approved within 365 days from the time that a convened IRB voted on approval, or approval pending minor modifications, or the date of the expedited review process if expedited review was performed, then the IRB Chair will send a letter to the investigator regarding the lapse in study approval which includes a strict warning regarding the importance of adhering to federal regulations. The principal investigator must submit the required information and documentation requested by the IRB to the IRB. Once the PI submits the required information, it will be reviewed as appropriate by the IRB. Principal investigators who fail to comply with continuing review timelines may be suspended from conducting research. This will be evaluated on a case by case basis.

n. **Submission of IRB Requested Modifications to Research Projects**
In cases where protocols are approved pending minor modifications, investigators are given a 60 day deadline to submit the required modifications to the IRB. This deadline may be extended provided that the investigator keep the Research Service office informed of the status of the protocol. The deadline may be extended in 60-day increments, for up to a total of 6 months. After the 6 month period, the investigator will receive a warning that if the requested modifications are not submitted within the next 7 days, the protocol will be administratively terminated. This action will require the investigator to submit the study as a new protocol for full review if they intend to pursue IRB approval. The IRB will consider exceptions to this policy only in extraordinary circumstances that may be out of the investigator's control. This circumstances may include: awaiting word regarding funding status, or awaiting changes being made by the sponsor, which may extend the time that an investigator needs to make required modifications.

o. **Suspension or Termination of IRB Approval of Research (38 CFR 16.113).**
All investigators conducting research as employees or agents in the PVAMC are required to notify the IRB promptly of any serious or continuing non-compliance with applicable regulatory requirements or with the determinations of the IRB.

The IRB may vote to suspend or terminate approval of research not being conducted in accordance with IRB or regulatory requirements or that has been associated with unexpected problems or serious harm to subjects.

The IRB shall notify the principal investigator in writing of such suspensions or terminations and shall include a statement of the reasons for the IRB's actions. The terms and conditions of the suspension must be explicit. The investigator shall be provided with an opportunity to respond in person or in writing.

Where the IRB Chairperson determines that such action is necessary to ensure the rights and welfare of subjects, the Chairperson may require an immediate, temporary suspension of enrollment of new

subjects or of continued participation of previously enrolled subjects, pending review of the situation by the convened IRB.

It is the responsibility of the IRB Chairperson and/or the ACOS/R&D to provide prompt written notification to the R&D Committee and to relevant Federal agencies, including ORO, OHRP, and FDA (for FDA-regulated research) of for-cause suspensions and terminations (e.g. associated with unexpected harm, research not being conducted in accordance with the IRB's requirements, and lack of continuing review) of IRB approved research projects. Routine study closures or study completions are not be reported to these agencies.

p. **Appeal of IRB Determinations (38 CFR 16.109(d)).** The IRB shall provide the PI with a written statement of its reasons for disapproving or requiring modifications in proposed research and shall give the PI an opportunity to respond. This correspondence will be provided to the PI within a reasonable time frame for items reviewed outside of a convened meeting. The PI or appropriate designee shall respond in writing for those items requiring a signature (such as a revised initial review questionnaire), but may submit other revisions electronically to the IRB Coordinator. A time frame and format for response will be provided on the IRB correspondence based on the nature of the requested response.

In such cases as there is a dispute between the IRB and the PI regarding required modifications to the protocol or other parts of the IRB application which can not be amicably resolved between the parties involved, an appeal to the R&D Committee may be made by either the PI or the IRB.

The R&D Committee may organize a meeting with the individuals noted above to discuss the issue at hand, and will arrange further meetings with the PI and the IRB or designee as needed. The R&D Committee will facilitate the discussion between the PI and the IRB. Final recommendations for approval remain under the purview of the IRB. The R&D Committee may want to comment on the process and make recommendations to the IRB for future protocols similar to the one under appeal.

7. Considerations During IRB Review and Approval

The IRB shall determine the following during the review and the approval of research, as stated in the Department of Veterans Affairs, Department of Health & Human Services, and Food & Drug Administrations regulations. Specifically, the IRB will determine that the criteria detailed in the following sections below (c, d, e, f, g (unless informed consent is waived in accordance with Federal regulations). m, n, o) are satisfied before approving research.

a. **Levels of Risk (38 CFR 16.102(i) and 110).**

The IRB must consider the overall level of risk to subjects in evaluating proposed research during the initial and continuing review of the research. The IRB identifies the risks to the subject. These risks are clearly identified in the informed consent form. The IRB determines the level of risk of a protocol by evaluating the nature of several types of risk, including but not limited to physical/medical risk, psychological, social, economic and risk of loss of privacy/confidentiality that could result from participation in the research. The IRB also evaluates the probability of the occurrence of a risk, as well as the severity of each potential risk in order to qualify each protocol as less than minimal, minimal, moderate or high risk. The IRB determines the interval for continuing review based on the level of risk of the research project.

The regulations require that the IRB distinguish research that is greater than minimal risk from research that is no greater than minimal risk, when considering proposals for expedited review and for vulnerable populations. However, the IRB assesses the risk/benefit in all research protocols.

The IRB uses the following criteria for determining whether or not the risks to the subjects are minimal: under VA regulations at 38 CFR 16.102(i), "**minimal risk** means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."

b **Implementing Flag Advisories in the Electronic Medical Record.**
Research studies which the IRB recognizes as moderate and/or high risk may require that a Research flag be activated in the patient's CPRS electronic medical record. Studies that generally require a flag are those that are invasive, including studies requiring surgery and/or utilizing investigational devices or drugs. Flags may also be required on studies for which the IRB feels it is important for any medical staff member working with an enrolled patient know that they are participating in a research study, for example, Post Traumatic Stress Disorder studies.

The Research Service will activate an electronic flag advisory for any project which the IRB requires a flag. An electronic record flag advisory is an electronic record flag, which serves as an immediately identifiable alert that promotes safe, appropriate, timely and respectful patient care. VISTA is programmed such that when patients with electronic record flags make scheduled or unscheduled visits to the medical center and clinics, the patient information display will show a screen with the established type of flag advisory highlight.

The Principal Investigator will be notified by the IRB Coordinators when the flag is ready to be applied. As patients are enrolled into the research protocol, the Principal Investigator will obtain a signed informed consent and enter the patient's name into the medical record flag advisory system. The Research Service is responsible for de-activating the research protocol flag when the study is concluded. However, the Principal Investigator is responsible for de-activating the research flag if a patient withdraws or participation ends prior to the termination of the study.

A patient may only be enrolled in one research study for which the IRB has required a flag advisory in the patient's electronic medical records. **Any** exceptions must be approved in advance by the Chair of the IRB

c. **Risks Minimized (38 CFR 16.111(a)(1)).**
To approve research, the IRB must determine at the time of initial and continuing review that risks are minimized by (1) using procedures that are consistent with sound research design and (2) do not expose subjects to unnecessary risks. Whenever appropriate, the research should utilize procedures that are already being performed on the subjects for diagnostic or treatment purposes.

The IRB examines the research plan, including research design and methodology, to determine that there are no obvious flaws that would place subjects at unnecessary risk. This includes the risk that the research is so poorly designed or is so lacking in statistical power that meaningful results cannot be obtained.

The IRB also considers the professional qualifications and resources of the research team as indicated on the IRQ. The PI must designate all co-investigators, collaborators, and study coordinators on the IRQ. In addition, in all studies that are outside the PI's medical specialty, the PI must designate a co-investigator or collaborator with expertise in the relevant medical specialty being studied. This co-investigator or collaborator will be in charge of all patient safety issues related to the checking of all laboratory/study testing in the research, following all laboratory/study results and communicating all moderate or severe results to the study participant, the study participant's primary care and specialty physicians, and assuring the accurate recording of all relevant laboratory/studies in the patient's electronic medical record.

Clinicians are expected to maintain appropriate professional credentials and licensing privileges. The IRB reserves the right to request additional information from investigators and participating physicians, such as curricula vitae, to assure that the qualifications of the research team are appropriate for the proposed study. Additional research staff working physically at the VA and/or having contact with VA patients must also be credentialed consistent with VA Office of Research & Development guidelines.

d. **Risks Reasonable Relative to Anticipated Benefits (38 CFR 16.111(a)(2)).**
To approve research, the IRB must determine at the time of initial and continuing review that the risks of the research are reasonable in relation to the anticipated benefits (if any) to subjects, and the importance of the knowledge that may reasonably be expected to result. This is determined at the time of initial and continuing reviews, as well as on an ongoing basis for other paperwork (such as amendments) submitted for each protocol. The IRB considers the following types of risks: physical, psychological, social and economic and determines the level of risks of the research. Probable individual and societal benefits of the research are also identified.

The IRB develops its risk/benefit analysis by evaluating the most current information about the risks and benefits of the interventions involved in the research, in addition to information about the reliability of this information. The IRB should consider only those risks that result from the research, and should not consider the long-range effects (e.g., public policy implications) of applying the knowledge gained in the research.

e. **Equitable Selection of Subjects (38 CFR 16.111(a)(3*)).***
The IRB determines by viewing the IRQ that the selection of subjects is equitable with respect to gender, age, class, etc. The IRB will not approve a study that does not provide adequately for the equitable selection of subjects.

This is the concept of “Justice” from the Belmont Report. In making this determination, the IRB evaluates: the purposes of the research; the research setting; scientific and ethical justification for including vulnerable populations such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons; the scientific and ethical justification for excluding classes of persons who might benefit from the research; and the inclusion/exclusion criteria.

f. **Circumstances of Informed Consent Requirements (38 CFR 16.111(a)(4) and 116).**
To approve research, the IRB must determine that legally effective informed consent shall be sought from each prospective subject or the subject's legally authorized representative (see 38 CFR 16.116), unless informed consent requirements can be waived or altered under VA regulations. All informed

consent forms and any such waiver must be consistent with applicable Washington and Oregon state law regarding content and participation in research.

Consistent with state law, VA policy recognizes as legally authorized representatives (1) persons appointed as health care agents under a Durable Powers of Attorney for Health Care; (2) court appointed guardians of the person; (3) next of kin in the following order: spouse, a majority of the adult children (18 years of age or older) who can be so located, parent, and a majority of the adult siblings (18 years of age or older) who can be so located. However, VA policy limits the conditions under which the IRB may approve the use of consent from legally authorized representatives. Informed consent may only be sought under circumstances that provide the subject (or the legally authorized representative) with sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence (38CFR16.116). These circumstances include:

(1) Assessing the prospective research participant's capacity to consent to the research protocol, prior to consenting the individual, to ensure that he/she is able to understand the study procedures and all risks and benefits in order to make an informed decision. The IRB may determine that for a high-risk study, procedures should be put in place to assess the research participant's capacity to consent.

(2) Presenting and ensuring the informed consent information is presented in a language that is understandable to the subject (or the subject's legally authorized representative).

(3) Excluding any exculpatory language from the informed consent process (a) through which the subject is made to waive, or appear to waive, any of the subject's legal rights; or (b) through which the investigator, the sponsor, the PVAMC, or the PVAMC's employees or agents are released from liability for negligence.

(4) Obtaining informed consent prior to initiation of any clinical screening procedures that are performed solely for the purposes of determining eligibility for research.

(5) Providing the prospective subject or the legally authorized representative sufficient opportunity to consider whether or not to participate.

(6) Ensuring that subjects give consent without coercion or undue influence.

The individual who informs the prospective research participant about the study and conducts the informed consent process must be knowledgeable about the study and be able to answer questions raised by the potential research participant or legally authorized representative. If the clinical investigator is unable to conduct the interview and informed consent process, then the clinical investigator may delegate this responsibility to an individual who is properly trained. Anyone conducting the informed consent process must fulfill the education requirements as stated in the PVAMC Human Research Protection Program Policy & Procedure, No. 4, located in Appendix L.

The required elements of an informed consent are stated in Section III. 8.

g. **Documentation of Informed Consent (38 CFR 16.117).**
To approve research, the IRB must determine that informed consent shall be appropriately documented, on VA Form 10-1086, properly executed with appropriate signatures of the subject or

legally authorized representative, witness, and person obtaining consent, date, time, and social security number as required by the IRB, unless documentation can be waived under VA regulations, the Common Rule, or FDA regulations. If the PI is not conducting the informed consent process, the PI must initial that he/she has reviewed the informed consent document and attest to the integrity of the informed consent process. The witness, except when informed consent is being obtained orally, is only witnessing the signature on the informed consent document and may not be involved in the research project at hand.

Informed consent must be obtained prior to entering a subject into a study and the conduct of any procedures required by the protocol, unless the informed consent requirement is waived by the IRB.

VA regulations at 38 CFR 16.117, the Common Rule, and FDA regulations provide two methods for documenting informed consent:

(1) Consent may be documented through use of a written consent document that embodies all of the required elements of informed consent (these elements are discussed in detail in Section III 8). The VA 10-1086 consent document form shall be used and must be signed by the subject (or the subject's legally authorized representative), and a copy must be given to the person signing the form. FDA regulations require that the signature be dated. This form may be read to the potential research participant or his/her legally authorized representative. The potential participant/legally authorized representative must be given adequate time to read the document and make a decision, regarding participation, prior to signing the informed consent document.

(2) Consent may also be documented through use of a "short form" written consent document, which states that the elements of informed consent have been presented orally to the subject (or the legally authorized representative) in a language understandable to the subject. The oral presentation must contain all of the information that is contained in the informed consent document. When this method is used the following is necessary:

(a) The IRB must approve a written summary of what is to be presented orally and the "short form" written consent document;

(b) There must be a witness to the oral presentation;

(c) The witness must sign both the "short form" and the written summary presented to the subject or legally authorized representative;

(d) Only the "short form" must be signed by the subject or the representative;

(e) The person obtaining the informed consent must sign the written summary; and

(f) A copy of the summary and the "short form" must be given to the subject or the representative.

PVAMC policy is that the original signed consent document must be forwarded to the Research Service within 48 hours of consenting the patient. The Research Service scans the consent form into

the patient's electronic record in the Computerized Patient Record System (CPRS). The Principal Investigator must maintain a copy of the signed consent form for the investigator's files. (M-3, Part 1, Chapter 9.11b(1)). A copy is also given to the subject and when applicable to the Research Pharmacy.

It is the responsibility of the Research Assurance and Compliance Coordinator to assure that this is being done appropriately. Results of internal audits and recommendations for corrective action, if needed, will be reported to the IRB and R&D Committee for deliberation.

h. **Witnesses of Informed Consent Process.** The IRB requires that a witness, a person unassociated with the research project for which an individual is consenting, be present during the:

(1) Signature of the written informed consent document, Section g (1) above. This witness does not need to witness the entire informed consent process, only the signing of the document. The witness must sign the written informed consent document.

(2) Informed consent process when a "short form" written consent is being used, Section g (2) above. The witness must sign both the short form written consent document and the summary orally presented to the subject or the subject's legally authorized representative.

i. **Consent Monitoring (M-3, Part 1, Chapter 9.09 (f)).** The IRB may monitor the consent process of any study which is currently active. An IRB member or designee may observe a consent session as an impartial observer or conduct a structured interviews of research participants.

In addition, informed consent documentation is reviewed and overseen through the following mechanisms: 1) the IRB or its designee, which may include the IRB Coordinators and/or staff, carefully review each signed informed consent form which is turned in for inclusion into the patient's CPRS record to assure that it was correctly completed and that all required signatures are in place. 2) the Quality & Performance Service conducts ongoing audits of informed consent documentation.

j. **Informed Consent Reading Level and Language (38 CFR 16.116).** VA regulations at 38 CFR 16.116, the Common Rule, and FDA regulations require that informed consent is at the appropriate reading level of the potential patient population and be obtained in a language that is understandable to the subject (or the subject's legally authorized representative).

In cases where informed consent must be obtained from non-English speakers, the Principal Investigator is responsible for working with the IRB to determine that an effective and appropriate method is in place. This may include the use of a reliable, certified translator or a certified translation of the informed consent document.

k. **Waiver of Documentation of Consent. (21CFR56.109(c))** VA regulations at 38 CFR 16.117(c) permit an IRB to waive the requirement to obtain written documentation of informed consent. *(Note: This provision can be used only for the waiver of documentation of consent, not for waiver or alteration of consent itself.)* To approve such a waiver, the IRB must find and document **either** of the following conditions:

(1) The only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. In this case, each subject may be asked whether the subject wants documentation linking

the subject with the research, and the subject's wishes will govern. (The waiver provision is **not** applicable to FDA-regulated research).

OR

(2) The research presents no more than minimal risk of harm to subjects and involves procedures or activities for which written consent is not normally required outside of the research context. In cases in which the documentation requirement is waived, the IRB may require the principal investigator to provide subjects with a written statement regarding the research. This policy is applicable to FDA-regulated research.

IRB minutes shall clearly reflect this waiver provision and the justification for its use. In addition, the IRB may also waive the Health Insurance Portability and Accountability Act of 1996 (HIPAA) requirements for an authorization for research purposes. In these cases, the IRB must additionally document the justification for its use. Please see HRPP Policy & Procedure, No.6, located in Appendix N.

l. **Waiver or Alteration of Informed Consent Requirements: Minimal Risk Research.** VA regulations at 38 CFR 16.116(d) permit the IRB to approve a consent procedure which does not include or which alters some or all of the required elements of informed consent, or to waive the requirement to obtain informed consent altogether. To approve such a waiver or alteration, the IRB must find and document that:

(1) The research involves no more than minimal risk to the subjects.

(2) The waiver or alteration shall not adversely affect the rights and welfare of the subjects.

(3) The research could not practically be carried out without the waiver or alteration.

(4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

These findings and their justifications shall be clearly documented in IRB minutes when the IRB exercises this waiver provision. This waiver provision is not applicable to research governed by FDA regulations, and the IRB cannot approve such alterations or waivers for FDA-regulated research (21 CFR 50.20).

The waiver or alteration of informed consent requirements for FDA regulated articles is described in Section V 1(p).

In addition, the IRB may also waive the Health Insurance Portability and Accountability Act of 1996 (HIPAA) requirements for an authorization for research purposes. In these cases, the IRB must additionally document the justification for its use. Please see HRPP Policy & Procedure, No.6, located in Appendix N.

m. **Review of Plans for Data and Safety Monitoring (38 CFR 16.111 (a)(6)).**

To approve research, the IRB determines that, where appropriate, the research plan makes adequate provision for monitoring the data to ensure the safety of subjects. For research in which risks are substantial, the IRB may require a general description of the data and safety-monitoring plan to be submitted to the IRB as part of the proposal. This plan should contain procedures for reporting adverse events (AEs).

In general, it is desirable for a Data and Safety Monitoring Board (DSMB) to be established by the study sponsor for research that is blinded, involves multiple sites, involves vulnerable subjects, or employs high-risk interventions. For some studies the National Institutes of Health (NIH) require a DSMB. The IRB has the authority to require a DSMB as a condition for approval of research where it determines that such monitoring is needed.

When DSMBs are utilized, IRBs conducting continuing review of research may rely on a current statement from the DSMB indicating that it has and will continue to review study-wide AEs, interim findings, and any recent literature that may be relevant to the research, in lieu of requiring that this information be submitted directly to the IRB.

n. **Privacy of Subjects and Confidentiality of Data (38 CFR 17.33(a) and (b)).** The IRB requires that subjects' confidentiality be strictly maintained. The IRB serves as the Privacy Board for Research at the Portland VA Medical Center and abides by the Health Insurance Portability and Accountability Act (HIPAA) of 1996 and the HRPP Policy & Procedure No. 6, located in Appendix N. The IRB recognizes the importance of protecting subject confidentiality, and carefully evaluates each protocol for the confidentiality measures taken. Only those authorized by the IRB, which may include: the Principal Investigator, Co-Investigator and Research Assistant(s), etc., shall be allowed access to individually identifiable patient data (protected health information, PHI). Individuals must have prior approval by the IRB before receiving individually identifiable patient data for research purposes. This may include requiring such measures as a set of research codes rather than the use of individually identifiable information, linked to the patient through only one codebook maintained by the Principal Investigator.

In reviewing confidentiality protections, the IRB shall consider the nature, probability, and magnitude of harms that would be likely to result from a disclosure of collected information outside the research. It shall evaluate the effectiveness of proposed anonymizing techniques, coding systems, encryption methods, storage facilities, access limitations, and other relevant factors in determining the adequacy of confidentiality protections.

o. **Additional Safeguards for Vulnerable Subjects (38 CFR 16.111(b) and M-3, Part 1, Chapter 9.09(a)(8)). For additional information regarding vulnerable subjects, please review Section IV. 4.**
The IRB carefully reviews at it's convened meetings studies which include vulnerable subjects. Vulnerable subjects include, but are not limited to prisoners, pregnant women, mentally disabled persons or economically or educationally disadvantaged persons, with the recognition that persons with impaired decisional capacity may also be included in the category as well as being in need of special protection.

The IRB must be cognizant of the vulnerable nature of many VA human subjects. To the extent that such subjects are economically dependent upon the VA for medical treatment; suffer from cognitive, affective, or other psychological afflictions, or have substance abuse problems, VA human subjects may be

particularly vulnerable to unintended, coercive or undue influences relative to participation in research (M-3, Part 1, Chapter 9.12). Likewise, persons who primarily look to the VA for treatment of their medical problems may not fully understand the implications of research participation, especially when it is offered by someone they consider a provider of clinical care.

At the time of initial review the IRB may determine and require that, when appropriate, additional safeguards be put into place for vulnerable subjects, such as those without decision-making capacity. The IRB may require that someone other than the primary care provider conduct the informed consent session and that additional measures for evaluating capacity to consent be in place. The IRB carefully evaluates each protocol to determine if vulnerable subjects are included in the study population and what measures have been taken to protect them. This feature is included in the IRB Reviewer Checklist included in Appendix E.

To approve research, the IRB determines that, where appropriate, additional safeguards have been included to protect the rights and welfare of subjects who are likely to be vulnerable to coercion or undue influence. This includes but is not limited to research with children (45 CFR 46 Subpart D), prisoners (45 CFR 46 Subpart C), pregnant women (45 CFR 46 Subpart B), persons with mental disabilities, or economically or educationally disadvantaged persons. The PVAMC does not conduct research with prisoners or fetuses.

See Section IV.4, regarding more details on research involving vulnerable subjects.

p. **Criteria for Requiring Review More Often than Annually (38 CFR 16.103(b)(4)(ii)).** The IRB may determine that a protocol should be reviewed more frequently than annually. This may be determined at any time for any reason, including level of risk, nature of adverse events, and study population.

The IRB may consider the following factors in determining the criteria for which studies require more frequent review and what the timeframes generally will be:

(1) Probability and magnitude (degree or risk) of anticipated risks to subjects.

(2) Likely medical condition of the proposed subjects.

(3) Overall qualifications of the principal investigator and other members of the research team.

(4) Specific experience of the principal investigator and other members of the research team in conducting similar research.

(5) Nature and frequency of adverse events observed in similar research at this and other facilities.

(6) Vulnerability of the population being studied.

(7) Other factors that the IRB deems relevant.

In specifying an approval period of less than 1 year, the IRB may define the period with either a time interval or a maximum number of subjects, i.e., after 3 months or after three subjects. The IRB documents in the minutes the determination of risk level for a research project and approval period.

q. **Independent Verification from Sources Other than the Investigator that No Material Changes Have Occurred Since the Previous IRB Review (M-3, Part 1, Ch. 9.09 (c)(2)).** The IRB recognizes that protecting the rights and welfare of subjects sometimes requires that the IRB verify independently, utilizing sources other than the investigator, that no material changes occur during the IRB-designated approval period. Independent verification from sources other than the investigator may be necessary at times, for example, in cooperative studies, or other multi-center research.

The IRB shall consider the following factors in determining which studies require such independent verification:

(1) Probability and magnitude of anticipated risks to subjects.

(2) Likely medical condition of the proposed subjects.

(3) Probable nature and frequency of changes that may ordinarily be expected in the type of research proposed.

(4) Prior experience with the principal investigator and research team.

(5) Other factors that the IRB deems relevant.

In making determinations about independent verification, the IRB may prospectively require that such verification take place at predetermined intervals during the approval period, or may retrospectively require such verification at the time of continuing review, review of amendments and/or adverse events.

If any material changes have occurred without IRB review and approval, the IRB will decide the corrective action to be taken.

r. **Audits of Research Protocols or Study Procedures.** The IRB or designee may audit a research protocol or study procedures at any time for any reason. The IRB will maintain documentation that such an audit occurred, the result of the audit, and, if a response was required from the principal investigator or other designated person, the response generated.

s. **Advertisements and Recruitment Incentives.** The IRB must approve any and all advertisements and recruitment incentives prior to posting and/or distribution. This information should be submitted to the IRB with the initial application or as an addendum to the protocol. The IRB reviews the material to assure that the material is accurate and is not coercive or unduly optimistic, creating undue influence to the subject to participate.

Any advertisement to recruit subjects should be limited to the information the prospective subjects need to determine their eligibility and interest. When appropriately worded, the following items may be included:

(1) The name and address of the clinical investigator and/or research facility.

(2) The condition being studied and/or the purpose of the research.

(3) In summary form, the criteria that will be used to determine eligibility for the study.

(4) The time or other commitment required of the subjects.

(5) The location of the research and the person or office to contact for further information.

(6) A clear statement that this is research and not treatment.

(7) A brief list of potential benefits (e.g. no cost of health exam).

Recruitment Incentives to the investigator from a sponsor may not create undue influence to recruit patients for a study and must be reasonable in relation to the work being performed.

t. **Payment to Research Subjects (M-3, Part 1, Chapter 9.13).** The IRB reviews any payment to research subjects at the time of the initial application to assure that the amount is not coercive given the nature of the research or creates undue influence on the subject to participate. The information is provided in the IRQ, and additional information may be required on an as needed basis.

Payments may not be provided to subjects on a schedule that results in coercion or undue influence on the subject's decision to continue participation. For example, payment may not be withheld as a condition of the subject completing the research. If the subject withdraws early, payment must be prorated to reflect the time and inconvenience of the subject's participation up to that point. The schedule, amount and conditions of payment must be stated in the informed consent form.

VA policy (M-3, Part 1, Chapter 9.13) prohibits paying subjects to participate in research when the research is an integral part of a subject's medical care and when it makes no special demands on the subject beyond those of medical care.

Payment may be permitted, with prior approval of the IRB, in the following circumstances however:

(1) **No direct subject benefit.** When the study to be performed is not directly intended to enhance the diagnosis or treatment of the medical condition for which the volunteer subject is being treated, and when the standard of practice in affiliated, non-VA institutions is to pay patients in this situation.

(2) **Others being paid.** In multi-institution studies, where patients at a collaborating non-VA institution are to be paid for the same participation in the same study at the same rate proposed.

(3) **Comparable situations.** In other comparable situations in which, in the opinion of the IRB, payment of patient volunteers is appropriate.

Investigators who wish to pay research subjects must indicate in their proposal the justification for such payment with reference to the criteria listed and, in addition, must:

(1) Substantiate that proposed payments are reasonable and commensurate with the expected contributions of the subject;

(2) State the terms of the subject participation agreement and the amount of payment in the informed consent form; and

(3) Substantiate that subject payments are fair and appropriate, and that they do not constitute (or appear to constitute) undue pressure on the veteran patient to volunteer for the research study.

The IRB shall review all proposals involving the payment of subjects (in excess of reimbursement for travel) in the light of these guidelines. The Research Service office must ensure that such payments to subjects are made from appropriate funds.

u. **Compensation for Injury (38CFR16.116 (a)(6), 17.85).** Information on compensation for injury must be included in all informed consent forms, with contact names and telephone numbers, per the requirements of the text of the informed consent form.

VA medical facilities shall provide necessary medical treatment to a research subject injured as a result of participation in a research project approved by a VA Research & Development Committee and conducted under the supervision of one or more VA employees.

However, this requirement does not apply to (1) treatment for injuries due to non-compliance by a subject with study procedures; or (2) research conducted for the VA under a contract with an individual or a non-VA institution.

For additional information, regarding exceptions to this information, please see 38CFR17.85.

v. **Certificates of Confidentiality.**
Where research involves the collection of highly sensitive information about individually identifiable subjects, the IRB may determine that special protections are needed to protect subjects from the risks of investigative or judicial processes. This is rare in VA, however, in such situations the IRB may require that an investigator obtain a Department of Health and Human Services (DHHS) Certificate of Confidentiality (CoC).

For studies not funded by DHHS, if there is an Investigational New Drug Application (IND) or an Investigational Drug Exemption (IDE), the sponsor can request a CoC from the FDA. The CoC was developed to protect against the involuntary release of sensitive information about individual subjects for use in federal, state, or local civil, criminal, administrative, legislative, or other legal proceedings.

An investigator must obtain a certificate of confidentiality in cases when the information gathered for the research could be held against the research participant in a court of law. A certificate of confidentiality may be obtained from the agencies involved in the study.

The CoC does not prohibit voluntary disclosure of information by an investigator, such as voluntary reporting to local authorities of child abuse or of a communicable disease. In addition, the CoC does not protect against the release of information to VA, DHHS or FDA for audit purposes. Consequently, the IRB may require that these conditions for release be stated clearly and explicitly in the informed consent document.

w. **Compliance with All Applicable State and Local Laws.** The IRB follows all applicable state and local laws in the states of Oregon and Washington. Included in Appendix G are the applicable state statutes.

All consent forms must be consistent with applicable state and local laws.

x. **IRB Considerations About Ethical Study Design.** The IRB takes into consideration the study design to assure that research ethics are being followed. This includes careful consideration of issues such as protection of privacy and confidentiality in epidemiological research, genetic research, and family research. Even studies which, by their epidemiological nature may not require an informed consent form, are carefully evaluated to assure that only the information needed is being gathered, that the confidentiality of the information is carefully protected, and that the risk to the patient remains minimal.

y. **IRB Considerations of Conflict of Interest.** Please see HRPP, Policy & Procedure No. 5, "Conflict of Interest in Human Research," regarding IRB considerations of conflict of interest. This policy may be found in Appendix M. The conflict of interest policy applies to all full-time and part-time employees, members of governing panel or board and paid or unpaid consultants participating in human subjects research approved by the PVAMC IRB.

z. **Principal Investigator Expertise.** Studies which go beyond the individual expertise of the principal investigator into other medical generalist or specialty areas, may require that the principal investigator make certain that he or she has identified a qualified co-investigator or collaborator who will be in charge of patient safety. Such patient safety issues here include: making certain that abnormal laboratory/study results are reviewed in a timely fashion, patients contacted about abnormal laboratory/study results in a timely fashion, and the abnormal laboratory/study results that could any patient injury are acted upon in an expedited manner. This co-investigator and collaborator will usually be involved in developing the scientific protocol section involving his or her area of expertise and training in making sure of optimal patient safety of follow-up of abnormal laboratory/study results. This co-investigator and collaborator will also be responsible with making all relevant communication to the patient's primary care provider about any new abnormalities of a moderate or severe nature and recording the same abnormalities in the patient's electronic medical record.

aa. **Long-Range Planning to Ensure Continuation of Research in the Event of the Absence of an Investigator**

This policy helps to ensure that when an investigator is called to active duty in times of war or national emergency, thus decreasing the number of staff available to conduct research, that the research will be conducted properly and more importantly, the proper treatment of the human subjects involved in the research will not be sacrificed.

If in the course of the research an investigator will be absent, the IRB must be notified, regarding the investigator's change in activity on the research project. The Principal Investigator or PVAMC

Responsible Investigator must verify to the IRB that the quality of the research being conducted and the safety and treatment of the human subjects involved will not be challenged, i.e. whether or not treatment of the research subjects currently enrolled will continue and how these subjects will be monitored for safety per protocol.

If the Principal Investigator or PVAMC Responsible Investigator will be absent, active recruitment of research subjects into the research study must be suspended until the PI/PVAMC Responsible Investigator returns or until the Principal Investigator/PVAMC Responsible Investigator appoints a new individual to assume the absent investigator's responsibilities and justifies their credentials to perform the related responsibilities. The individual(s) must complete the required education requirements and be credentialed and privileged to perform the absent investigator's responsibilities.

If a co-investigator will be absent, active recruitment in the research project does not need to be suspended, unless the individual's role in the research was essential and the individual will not be replaced while he/she is absent. If the co-investigator will be replaced, the individual(s) must complete the required education requirements and be credentialed and privileged to perform the absent co-investigator's responsibilities.

bb. **Significant New Findings.**
During the course of research, significant new knowledge or findings about the medication or test article and/or the condition under study may develop. Since the new knowledge or findings may affect the risks or benefits to subjects or subjects' willingness to continue in the research, the IRB may require during the ongoing review process that the Principal Investigator contact the currently enrolled subjects to inform them of the new information. The IRB will communicate this to the Principal Investigator. The informed consent should be updated and the IRB may require that the currently enrolled subjects be re-consented, acknowledging receipt of this new information and for affirming their continued participation.

cc. **Changes in IRB Approved Research Protocols**
All modifications in IRB approved research protocols, including even minor changes, must be submitted to the IRB for review and approval prior to initiation, except when necessary to eliminate apparent immediate hazards to the subject. The mechanisms in place to ensure that these changes are reported promptly and not initiated without IRB approval, except in the above stated circumstance, include 1) verifying at the time of continuing review that no changes have been made to the research project without prospective IRB approval; 2) investigator initiated submission of changes through the Project Revision Amendment Form (PRAF) followed by IRB review; and 3) review of informed consent documents as they come into the Research Service office to be scanned into the CPRS.

dd. **Credentialing and Education Verification for New Human Subjects Research Projects**
The Research Assurance & Compliance Coordinator will monitor new human subjects research projects as they are received by the Research Service office. All individuals involved in human subjects research at the VA Medical Center or having contact with VA patients must be credentialed and have completed the required education, prior to working on the research project. This is consistent with the 2003 Stand Down Requirements. Please see the flow diagram in Appendix S.

8. **Required Elements of Informed Consent (38CFR16.116; M-3 Part I, Chapter 9.11.b.2.a & Appendix 9.C.2**

One overarching requirement of research involving human subjects is that investigators must obtain the legally effective or the subject's legally authorized representative informed consent of prospective subjects **before** they can be included in any procedures required by the protocol. Informed consent presumes two simultaneous concepts: informed decision-making and voluntary participation. Prospective subjects must be given sufficient information about the research and its risks and benefits to reach an **informed decision** as to whether they will **voluntarily participate.**

Informed consent is an ongoing process of information exchange between the prospective research participant and trained individual conducting the consent process, not simply a signed consent form. Prospective research participants must be fully informed of the research procedures PRIOR to agreeing to participate in the study. The consenting process begins with the information given during subject recruitment, as well as oral instructions, the written informed consent form and other materials, the ability for the individual to ask questions, the signed written agreement by the subject or legal representative and in the future if the subject has additional questions, concerns, or if the study presents new data necessary to present to the subject.

The IRB prohibits the informed consent, written or oral, from containing any exculpatory language through which the subject or the legally authorized representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.

The IRB requires that the information given to the subject or their legally authorized representative is in a language that is understandable to the subject or representative. Appropriate reading level for the informed consent is an eighth grad reading level. In addition, translated consents must be available for non-English speaking participants, in a translation that they understand.

To ensure an effective informed consent process, Department of Veterans Affairs (VA) regulations at 38 CFR 16.116(a), the Common Rule, and Food and Drug Administration (FDA) regulations mandate the inclusion of the following fundamental informed consent elements and the additional elements when appropriate. Depending on the nature of the research (38 CFR 16.116(b)), an investigator may request elimination of any of the elements depending on the nature of the research.

The PVAMC requires that the informed consent be on VA Form 10-1086, be at the appropriate reading level of the target participants, and include the following elements as set forth in VA and other regulations, except when specified elements have been waived from the informed consent requirements. Informed consent form templates and checklists are located in Appendix H.

a. **Fundamental Required Elements**

(1) **Research Statement, Purpose, and Procedures.**

(a) A statement that the study involves research;

(b) An explanation of the purposes of the research;

(c) An explanation of the expected duration of subjects' participation;

(d) A description of the procedures to be followed; and

(e) Identification of any procedures that are experimental.

(2) **Description of any Reasonably Foreseeable Risks or Discomforts to the Subject.**
Informed consent information must describe any reasonably foreseeable risks or discomforts associated with the research. Risks may include physical, psychological, social or economic risks.

(3) **Reasonably Expected Benefits to Subjects or Others.**
Informed consent information must describe any benefits to subjects or to others that may reasonably be expected from the research. However, care must be taken not to overstate the benefits and create an undue influence on subjects. Payment for subject's participation in a research project is not to be considered as a benefit of the research.

(4) **Appropriate Alternatives to Participation.**
Informed consent information must include a disclosure of any appropriate alternative procedures or courses of treatment that may be advantageous to the subject. Enough detail must be presented so that the subject can understand and appreciate the nature of any alternatives. It is not sufficient simply to state, "the doctor will discuss alternatives to participating."

(5) **Extent of Privacy and Confidentiality.**
Informed consent information must describe the extent to which confidentiality of records identifying the subject will be maintained. Research often poses the risk of loss of confidentiality to subjects who participate. Many persons who would not otherwise have access to identifiable, private information about the subject may be involved in the research process. Consent information should describe any procedures that the research team will use to protect subjects' private records. In some research, loss of privacy may be the greatest risk of participation. For FDA regulated studies, consent forms must included that the FDA may inspect research records, Section 8b. (7).

Research projects which will combine the HIPAA Authorization requirements into the informed consent form will require 9 additional elements be added to the informed consent form. Please refer to the HRPP Policy and Procedure, No.6, regarding the additional elements required if the HIPAA Authorization.

(6) **Compensation or Treatment for Injury.**
In formed consent information for research involving more than minimal risk must include explanations regarding:

(a) Whether any compensation is available if injury occurs.

(b) In accordance with Federal law, a statement that veteran-subjects shall receive medical care and treatment for injuries suffered as a result of participating in a VA research program and whether any medical treatments are available if injury occurs.

(c) A description of any such compensation or treatments or where more information about them is available.

(7) **Contact Information.**
Informed consent information must include details, including telephone numbers, about whom to contact for three specific situations:

(a) For answers to questions about the research. The principal investigator and other members of the research team are appropriate contacts for this information.

(b) For answers to questions about subjects' rights contact information. The IRB Chairs are appropriate contacts for this information.

(c) In the event of a research-related injury occurs to the subject. The IRB Chairs, VA Regional Counsel and the Investigators are all appropriate contacts for this information.

(8) **Voluntary Participation Statement.**
It is particularly important in the VA context for subjects and prospective subjects to understand and have complete confidence that failure to participate will not jeopardize their VA provided care. Informed consent information must contain clear statements of the following:

(a) Participation in the research is voluntary.

(b) Refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled.

(c) The subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

(9) **Payment for Treatment (M-3, Part 1, Chapter 9, Appendix 9C).** Informed consent information must include a statement that veteran-subjects shall not be required to pay for treatment received as a subject in a VA research program. Investigators should note, however, that veterans in the "discretionary work load" category are subject to co-payments, if so indicated by a means test.

b. **Additional Elements Where Appropriate.**
Where appropriate, the VA regulations require that one or more of the following eight additional elements are included in the informed consent information:

(1) **Unforeseeable Risks to Subjects, Embryos, or Fetuses.** Some research involves particular procedures or interventions that may result in unforeseeable risks to subjects, to the embryo, or the fetus (if the subject is or may become pregnant). For research of such a nature, the informed consent information must warn subjects that some risks are currently unknown.

(2) **Investigator-Initiated Termination of Participation.**
There may be instances that would require investigators to terminate the participation of particular subjects (e.g., subject non-compliance with research, subject not benefiting from research). The informed consent information must specify these circumstances.

(3) **Additional Costs.**
If subjects must bear any additional costs (transportation, time away from work, health costs, etc.), these must be disclosed in the informed consent information. Any such costs must be consistent with Federal laws concerning veterans' eligibility for medical care and treatment.

(4) **Early Withdrawal/Procedures for Termination**.

Subjects have the right to withdraw from the research. However, some studies involve medications or procedures that would be dangerous for subjects to discontinue abruptly. For studies of this nature, the informed consent information must provide subjects with knowledge of the consequences affecting a decision to withdraw. In addition, if there are procedures regarding how to withdraw safely from the research, these must also be described. It is not appropriate for research staff to administer any additional research-oriented questionnaires or interventions that do not affect the safety of subjects who have decided to withdraw.

(5) **Significant New Findings.**
During the course of research, significant new knowledge or findings about the medication or test article and/or the condition under study may develop. Since the new knowledge or findings may affect the risks or benefits to subjects or subjects' willingness to continue in the research, the informed consent information must detail the procedures for contacting subjects regarding this new information and for affirming their continued participation.

(6) **Approximate Number of Subjects.** For certain types of research, the informed consent information should disclose the approximate number of subjects to be enrolled.

(7) **FDA Regulated Studies.**
If the research involves a drug with an Investigational Drug Exemption or Investigational Device Exemption, the following verbatim statement is required: "I have been informed that because this study involves articles regulated by the FDA, the FDA may choose to inspect research identifying me as a subject of this investigation."

(8) **Payment for participation.** The informed consent information should include a clear statement describing any payment the subject is to receive for participation, the required conditions for payment, and the payment schedule. Since VA regulations at 38 CFR 16.116(a)(8), the Common Rule, and FDA regulations all state that subjects may withdraw from research at any time without penalty of loss of benefits to which they are otherwise entitled, completing the research may not be made a condition of payment. For this reason there should be a description of how payment will be prorated and calculated for subjects who withdraw early.

d. **Human Biological Specimen Consent Form Requirements (VHA Directive 2000-043).**
Research projects collecting human biological specimens must contain the following elements:

(1) If the researcher believes that bodily fluids, substances or tissues of a research subject could be part of or lead to the development of a commercially valuable product, the following verbatim statement is required. "I authorize the use of my bodily fluids, substances, or tissues."

(2) Statement of whether or not the specimen will be used for future research and allow the choice of how the specimen will be used (any research, research by the PI, or other researchers, genetic analysis, research related to specific area, etc.).

(3) Whether or not the research results of future use of the specimen will be conveyed to the subject.

(4) Whether or not the subject will be re-contacted after the original study is completed.

(5) If the subject requests, the specimen and all links to the clinical data will be destroyed.

IV. SPECIAL CONSIDERATIONS FOR SPECIAL TYPES OF RESEARCH

1. Behavioral and Social Sciences Research.

This type of research often involves surveys, observational studies, personal interviews, or experimental designs involving exposure to some type of stimulus or intervention. This section discusses when exemption and expedited review are appropriate for some of these types of research.

a. **Social and Psychological Harms.** When evaluating behavioral and social science research, the IRB should carefully examine the research to determine the probability of risk of harm to subjects, especially with respect to social or psychological harm. This includes, but is not limited to the following:

(1) The IRB should consider the potential for participants to experience stress, anxiety, guilt, or trauma that can result in genuine psychological harm.

(2) The IRB should also consider the risks of criminal or civil liability or other risks that can result in serious social harms, such as damage to financial standing, employability, insurability, or reputation; stigmatization; and damage to social or family relationships.

(3) If information is being collected on living individuals other than the primary "target" subjects the IRB should consider the risk of harm to those "non-target" individuals, as well. “Non-target” individuals may include members of the subject’s family.

To mitigate such risks, the IRB should review the proposal for appropriate preventive protections and debriefings, adequate disclosure of risks in the informed consent information, and mechanisms to protect the confidentiality and privacy of persons participating in or affected by the research.

b. **Privacy and Confidentiality Concerns.** The use of confidential information is an essential element of much social and behavioral research. It is important to ensure that the methods used to identify potential research subjects or to gather information about subjects do not invade the privacy of the individuals. In general, identifiable information may not be obtained from private (non-public) records without the approval of the IRB and the informed consent of the subject. This is the case even for activities intended to identify potential subjects who will later be approached to participate in research. However, there are circumstances that are exempt from the regulations, and circumstances in which the IRB may approve a waiver of the usual informed consent requirements.

It is also important to ensure that adequate measures are taken to protect individually identifiable private information once it has been collected to prevent a breach of confidentiality that could lead to a loss of privacy and potentially harm subjects.

The IRBs serve as the Privacy Boards for Research at the Portland VA Medical Center and abide by the Health Insurance Portability and Accountability Act (HIPAA) of 1996 and the HRPP Policy & Procedure No. 6, located in Appendix N. The IRBs recognize the importance of protecting subject confidentiality, and carefully evaluate each protocol for the confidentiality measures taken.

c. **Safeguarding Confidentiality.** When information linked to individuals will be recorded as part of the research design, the IRB should ensure that adequate precautions shall be taken to safeguard the confidentiality of the information. The more sensitive the data being collected, the more important it is for the researcher and the IRB to be familiar with techniques for protecting confidentiality. The IRB may require that an investigator obtain a Department of Health and Human Services (DHHS) Certificate of Confidentiality (CoC). The CoC protects against the involuntary release of sensitive information about individual subjects for use in Federal, state, or local civil, criminal, administrative, legislative, or other legal proceedings.

d. **Research Involving Deception or Withholding of Information.** Sometimes, in psychological or educational research deception is necessary to prevent participant bias. When the IRB reviews research projects involving incomplete disclosure or deception, it must apply both common sense and sensitivity to the review.

Where deception is involved, the IRB needs to be satisfied that the deception is necessary and that, when appropriate, the subjects shall be debriefed. (Debriefing may be inappropriate, for example, when the debriefing itself would present an unreasonable risk of harm without a corresponding benefit.) The IRB should also make sure that the proposed subject population is suitable.

Deception can only be permitted where the IRB documents that a waiver of the usual informed consent requirements is justified under the criteria present in VA regulations and the Common Rule and 38 CFR 16.116(d). Specifically, the IRB must find and document that all four of the following criteria have been satisfied:

(1) The research presents no more than minimal risk to subjects.

(2) The waiver or alteration shall not adversely affect the rights and welfare of the subjects.

(3) The research could not practicably be carried out without the waiver or alteration.

(4) Where appropriate, the subjects shall be provided with additional pertinent information after participation.

In making the determination to approve the use of deception under a waiver of informed consent, the IRB should consider each criterion in turn, and document specifically (in the minutes of its meetings and/or in the IRB protocol file) how the proposed research satisfies that criterion.

2. **Research Using Data and Specimens.**

Many studies combine characteristics of behavior and social research with characteristics of biomedical research. There are many interdisciplinary combinations of behavioral and medical research. These types of studies often use or create tissue, specimen, or data repositories (banks). The following is guidance for the IRB when considering these types of studies.

a. **Prospective Use of Existing Materials.** Prospective studies are designed to observe outcomes or events (e.g., diseases, behavioral outcomes, or physiological responses) that occur subsequent to identifying the targeted group of subjects, proposing the study, and initiating the research.

(1) Prospective studies using materials (data, documents, records or specimens) that will "exist" in the future because they will be collected for some purpose unrelated to the research (e.g., routine clinical care) do not qualify for **exemption** under VA regulations at 38CFR16.101 (b)(4) because the materials in these studies are not in existence at the time the study is proposed and initiated.

b. **Retrospective Use of Existing Materials**. Retrospective studies involve research conducted by reviewing materials (data, documents, records, or specimens) collected in the past (e.g., medical records, school records, or employment records) and existing at the time the research is proposed and initiated.

(1) Such research may be exempt under Department of Veterans Affairs (VA) regulations at 38CFR16.101 (b)(4) if the information is publicly available or if the information is recorded in such a manner that subjects cannot be identified, either directly or through identifiers linked to the subjects.

(2) If not exempt, the IRB may review such research utilizing expedited procedures, provided that the research involves no more than minimal risk to subjects.

(3) However, retrospective studies using existing materials occasionally entail significant, greater than minimal risks and require review by the convened IRB (e.g. where the research reveals previously undisclosed illegal drug use and the expedited review raised concerns about invasion of subjects' privacy and/or the adequacy of confidentiality protections proposed by the investigators).

c. **Research Utilizing Large Existing Data Sets.**
The use of large, existing data sets requires IRB review when they contain identifiable private information about individuals. In such cases, the IRB must determine whether the information can be used without additional informed consent from the subjects.

- **Existing Data or Specimens:** these materials must be “on the shelf” (or in the freezer) at the time the protocols is initiated.
- **Indentifiable Private Information:** the identity of the individual is or may be readily ascertained by the investigator or associated with the information, even through the use of a code book. This may include names, Social Security numbers or pathology accession numbers.

(1) In making this determination, the IRB should first examine the conditions of informed consent under which the data were originally obtained. It may be that the proposed research is permissible under the original terms of consent.

(2) If this is not the case, then the IRB should consider whether it is permissible to waive the usual informed consent requirements in accordance with 38 CFR 16.116(d).

(3) In other cases, the IRB may determine that the research can proceed only if the investigator obtains and uses "anonymized" data. Under this scenario, codes and other identifiers are permanently removed from the data set before the data are sent to the investigator, and the removal is accomplished in such a manner that neither

the investigator nor the source maintaining the data set can re-establish subjects' identities.

(4) An alternative to anonymizing data is to maintain the data set as a data repository under the guidelines established by the Office for Human Research Protections (OHRP) and VA.

(5) **Research Utilizing Data or Tissue Banks (also called Repositories).** Human data repositories collect, store, and distribute identifiable information about individual persons for research purposes. Human tissue repositories collect, store, and distribute identifiable human tissue materials for research purposes.

- **Human Biological Specimens**: are defined in the VHA Directive 2000-043 as "any material derived from human subjects, such as blood, urine, tissues, organs, hair nail clippings, or any other cells or fluids, whether collected for research purposes or as residual specimens from diagnostic, therapeutic, or surgical procedures."

VA policy "Banking of Human Research Subjects' Specimens," VA Directive 2000-043 and ORO (aka ORCA) Guidance #19, specifies that human biological specimens, as well as the linked clinical data collected as part of research projects conducted by VA investigators in VA facilities or approved off-site locations, must be maintained at VA-approved tissue banks, whether the research is funded or un-funded, and regardless of the funding source.

Data/Tissue Bank activities involve three components: (a) the **collectors** of data or tissue samples; (b) the **bank/repository** storage and data management center; and (c) the **recipient** investigators. Under a repository arrangement, the IRB formally oversees all elements of repository activity, setting the conditions for collection, secure storage, maintenance, and appropriate sharing of the data and/or tissues with external investigators. Specifically, the IRB determines the parameters for sharing data and/or tissues (which are identifiable within the repository) in a manner such that additional informed consent of subjects is, or is not, required.

Typically, these parameters may involve formal, written agreements between the investigator and the tissue repository stipulating conditions as follows:

(1) The repository shall not release any identifiers to the investigator.

i. The investigator shall not attempt to recreate identifiers, identify subjects, or contact subjects.

ii. The investigator shall use the data only for the purposes and research specified.

iii. The investigator shall comply with any conditions determined by the repository IRB to be appropriate for the protection of subjects.

(2) Studies for which PVAMC investigators are collaborating with outside researchers and only analyzing anonymized tissue samples, i.e. not recruiting patients or obtaining informed consent, then the PVAMC IRB must review the protocol

approved by the collaborating institution's IRB. The PVAMC IRB may waive the informed consent requirement for the PVAMC collaborator's portion of the research project application.

3. **IRB Considerations about Ethical Study Design**

a. **Epidemiological Research.** Epidemiological research often makes use of sensitive, individually identifiable, private information (usually obtained from medical or other private records), and links this information with additional information obtained from other public or private records, such as employment, insurance, or police records. Epidemiological research may also combine historical research with survey and interview research. Epidemiological studies often present significant problems regarding both **privacy and confidentiality.**

(1) The IRB must first consider privacy issues, and must satisfy itself that the research does not constitute an unwarranted invasion of the subjects' privacy. In doing so, the IRB shall seek to establish that the investigator has legitimate access to any identifiable information that is to be utilized. For example, if State disease registry information is to be utilized, the IRB will need to examine State law relative to the legitimate release of such information for research.

(2) Once the IRB's privacy concerns have been resolved, the IRB will examine mechanisms for maintaining the confidentiality of data collected. The IRB shall seek to establish that confidentiality protections are appropriate to the nature and sensitivity of the information that has been obtained. Confidentiality protections will be in accordance with HIPAA.

(3) Because epidemiological research typically requires large numbers of subjects, investigators almost always request that the IRB waive the usual requirements for informed consent. To approve such a waiver in epidemiological research, the IRB must find and document that the criteria for a waiver of informed consent have been met (38 CFR 16.116(d)).

b. **Issues in Genetic Research.** Information obtained through genetic research may have serious repercussions for the subject or the subject's family members. Genetic studies that generate information about subjects' personal health risks can provoke anxiety and confusion, damage familial relationships, and compromise the subjects' insurability and employment opportunities. For many genetic research protocols, these psychosocial risks can be significant enough to warrant careful IRB review and discussion. Those genetic studies limited to the collection of family history information and blood drawing are not automatically classified as "minimal risk" studies qualifying for expedited IRB review. The addition of the genetic analysis can radically alter the level of risk.

The protection of private information gathered for and resulting from genetic research is a major concern. The IRB expects the investigator to describe in detail how individual privacy will be protected and how the confidentiality of obtained information will be maintained.

c. **Family History Research.** Family history research is a common technique used in bio-social and bio-behavioral research. Family history research typically involves obtaining information from one family member about other family members (third parties).

(1) It is important to recognize the VA regulations at 38 CFR 16.102 (f)(2) include in the definition of human subject a living individual about whom an investigator obtains "identifiable private information." Thus, the family members (third party) identified and described by their family member may be human subjects under the regulations if the investigators obtain identifiable private information about them.

(2) The IRB must determine whether family members (third parties) are human subjects in such research, and if so, consider the possible risks involved, and determine whether their informed consent is required or can be waived under the conditions specified at 38 CFR 16.116(d). There is not total consensus in the available guidance on this issue. OHRP representatives have advised that "third parties" about whom identifiable and private information is collected in the course of research are human subjects. Confidentiality is a major concern in determining if minimal risk is involved. The IRB can consider if informed consent from third parties can be waived in accordance with Section 116 and if so, document that in the IRB minutes. In most cases waiver of consent may be appropriate.

d. **Research Involving Potentially Addictive Substances.** Research involving potentially addictive substances often involves the use of what may be termed "abuse- liable" substances. Abuse-liable substances are pharmacological substances that have the potential for creating abusive dependency. Abuse-liable substances can include both legal and illicit drugs. The following are among the issues that the IRB should consider when reviewing research involving potentially addictive substances:

(1) When this type of research is proposed, the IRB must consider the subjects' capacity to provide continuous informed consent, ensuring that subjects are competent and are not coerced.

(2) If such research involves subjects that are institutionalized, the subjects' ability to exercise autonomy could be impaired.

(3) The IRB must also consider the requirements for equitable selection of subjects and protections for maintaining confidentiality, as such a population may be at risk for being discriminated against, or over-selected.

(4) The IRB must be sensitive to the ethical context of the research, in that there may be moral dilemmas associated with the use of placebos, or in cases where addicts are presented with alcohol and/or drugs.

(5) It is critical that the IRB focus on the considerations of risk and benefits of such research.

4. **Potentially Vulnerable Subject Groups**

Department of Veterans Affairs (VA) regulations at 38 CFR 16.111 (b) and Food and Drug Administration (FDA) regulations require the IRB to give special consideration to protecting the welfare of particularly vulnerable subjects, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons. Because veterans have a

history of obeying orders and making sacrifices, and because some veterans may not have access to other health care, some might consider veterans a potentially vulnerable population.

The IRB is also required to ensure that it has adequate representation on the Board to consider specific kinds of research involving these vulnerable populations in a satisfactory manner.

a. **Elements to Consider in Reviewing Research Involving Vulnerable Subjects.** The IRB must pay special attention to specific elements of the research plan when reviewing research involving vulnerable subjects.

(1) Strategic issues include inclusion and exclusion criteria for selecting and recruiting participants; informed consent and willingness to volunteer; coercion and undue influence; and confidentiality of data.

(2) The IRB carefully considers group characteristics, such as economic, social, physical, and environmental conditions, to ensure that the research incorporates additional safeguards for vulnerable subjects.

(3) Investigators are not permitted to over-select or exclude certain groups based on perceived limitations or complexities associated with those groups. For example, it is not appropriate to target prisoners as research subjects merely because they are a readily available "captive" population.

(4) The IRB is knowledgeable about applicable state or local laws that bear on the decision-making abilities of potentially vulnerable populations. Some of the issues addressed in Oregon and Washington State statutes are related to competency to consent, legally authorized representatives, and the age of majority for consent.

(5) Just as in providing medical care, research studies that plan to involve any potentially vulnerable populations must have adequate procedures in place for assessing and ensuring subjects' capacity, understanding, and informed consent or assent. When weighing the decision whether to approve or disapprove research involving vulnerable subjects, the IRB shall look to see that such procedures are a part of the research plan. In certain instances, it may be possible for researchers to enhance understanding for potentially vulnerable subjects. Examples include requiring someone not involved in the research to obtain the consent, the inclusion of a consent monitor, a subject advocate, interpreter for hearing-impaired subjects, translation of informed consent forms into languages the subjects understand, and reading the consent form to subjects slowly and ensuring their understanding paragraph by paragraph.

(6) The IRB may require additional safeguards to protect potentially vulnerable populations. For instance, the IRB requires that the investigator submit each signed informed consent form to the IRB. The IRB may also require that someone from the IRB oversee the consent process, or that a waiting period be established between initial contact and enrollment to allow time for family discussion and questions.

b. **Pregnant Women, Fetuses, and Human In Vitro Fertilization.** The Department of Health and Human Services (DHHS) regulations at 45 CFR Part 46, Subpart B detail special protections for research involving pregnant women, fetuses, and human in vitro fertilization. Under these regulations, the IRB is required to document specific findings to minimize the potential for risk or harm to the fetus, and additional attention must be given to the conditions for obtaining informed consent.

Unilateral exclusion of non-pregnant women of reproductive potential from research is not permitted by the IRB. However, given compelling scientific justification this option may be considered by the IRB. Where such justification exists, it may also be appropriate to exclude men of reproductive potential.

In general, Subpart B requires that research involving pregnant women and fetuses should involve the least possible risk. Persons engaged in the research may have no part in matters relating to the termination of the pregnancy, or to determine the viability of the fetus. No inducements may be offered to terminate a pregnancy.

Four separate conditions, each with their own requirements and IRB determinations, apply to research with pregnant women and fetuses, as outlined below.

(1) **Research Involving Pregnant Women.** Pregnant women may be involved as a subject in research as long as either of the following conditions apply: the purpose of the activity is to meet the health needs of the mother, and the fetus shall be placed at risk only to the minimum extent necessary to meet such needs; OR the risk to the fetus is minimal. The IRB determines that appropriate precautionary procedures are in place to ensure the nature of the study could not place the fetus at more than minimal risk. The mother and the father must be legally competent and provide consent, unless the purpose of the research is to meet the health needs of the mother, or the father is not reasonably available, or the pregnancy resulted from rape.

(2) **Research Directed Toward the Fetus In Utero.** The PVAMC does not conduct research directed toward the fetus in utero.

(3) **Research Involving the Fetus Ex Utero**. The PVAMC does not conduct research directed toward the fetus ex utero.

(4) **Research Involving Dead Fetuses, Fetal Material, or the Placenta**. The PVAMC does not conduct research involving dead fetuses, fetal material or the placenta.

c. **Research Involving Prisoners.** The PVAMC does not conduct research involving prisoners.

d. **Research Involving Children.** The VA is authorized to care for veterans and to conduct research that enhances the quality of health care delivery to veterans and is not authorized to care for the offspring of veterans. VA policy stipulates that children cannot be included in VA approved research unless a waiver has been granted by the Chief Research and Development Officer (VA Directive 2001-028, dated April 27, 2001).

e. **Research Involving Decision Impaired Subjects.** Decision impaired persons are individuals who have a diminished capacity for judgment and reasoning due to a psychiatric, organic, developmental,

or other disorder that affects cognitive or emotional functions. Other individuals who may be considered decision impaired, with limited decision-making ability, are individuals under the influence of or dependent on drugs or alcohol, those suffering from degenerative diseases affecting the brain, terminally ill patients, and persons with severely disabling physical handicaps.

There are no regulations specific to research involving cognitively impaired persons. However, there are specific VA policies that require certain findings to be made before persons incompetent to consent may be enrolled in research with the permission of a surrogate.

In all cases, the IRB takes special care to consider issues such as the selection of subjects, privacy and confidentiality, coercion and undue influence, and risk-benefit analysis. Decisions should be made with the utmost deference to the ethical principles underlying human subjects research as set forth in the Belmont Report. Capacity should be evaluated on an individual basis to avoid incorrect assumptions as to an individual's ability to make decisions. In cases where research involving cognitively impaired individuals is approved, the IRB may require additional safeguards (e.g., involvement of subject advocates, independent monitoring, formal capacity assessment, waiting periods) as part of the research plan to protect participants.

VA policy (Cooperative Studies Program Guidance) limits the conditions under which consent from legally authorized representatives (i.e., surrogate consent) can be obtained in lieu of consent from the subject. Consistent with state law, VA policy (M-3, Part 1, Chapter 9.12) recognizes as legally authorized representatives those stated in Section II, 3, Key Definitions, "Legally Authorized Representative," on page 3 of this SOP.

Surrogate consent may be used only when the prospective subject is incompetent as determined by two VA physicians, after appropriate medical evaluation, and there is little or no likelihood that the subject will regain competence within a reasonable period of time, or as established by legal determination. This definition of incompetence is not limited to the legal definition but also may also be a clinical judgment that a person lacks the capacity to understand the circumstances of participating in research and to make an autonomous decision to take part.

Before incompetent persons may be involved in any VA research, the IRB must find and document in writing that the proposed research meets all of the following conditions:

(1) **Only incompetent persons are suitable.** Competent persons are not suitable for the proposed research. The investigator must demonstrate that there is compelling reason to include incompetent persons as subjects. Incompetent persons must not be involved as subjects simply because they are readily available.
(2) **Favorable Risk/Benefit Ratio.** The proposed research entails no significant risks, or if the research presents risk of harm, there must at least be a greater probability of direct benefit to the subject than of harm.
(3) **No Resistance.** Subjects do not resist participating. Under no circumstances may subjects be forced or coerced into participating.
(4) **Well-Informed Representatives.** Procedures have been devised to ensure that subjects' representatives are well informed regarding their roles and obligations to protect the rights and welfare of the subjects they represent. Representatives must be informed in writing that their obligation is to try to determine what the subject

would do if competent, or if the subject's wishes cannot be determined, what is in the subject's best interests.

f. **Research Involving PVAMC Employees, Students and Trainees.**
These individuals may also be considered vulnerable subjects. Thus, the IRB upholds the standards in approving research involving these groups as other vulnerable subjects research. The IRB takes into consideration undue influence that an employee may experience as being approached for participating in a research project. The IRB ensures that no employees, students, or trainees feel obligated to participate in research in order to avoid loss of employment or privileges. Investigators, who would like to recruit VA employees for a research project, may be required to obtain approval from the local American Federation of Government Employees (AFGE).

g. **Human Fetal Tissue Transplantation Research.** The PVAMC does not conduct research with human fetal tissue transplantation.

h**. Research Involving Deceased Persons.** In the rare cases that such studies are proposed, the IRB will review such research projects involving deceased persons by evaluating the nature of the research and determining if consent of family members is necessary, or whether the body may be treated in the same manner as that of donated tissue. The IRB also ensures that appropriate confidentiality measures are in place.

Under HIPAA, investigators who propose research involving decedent's protected health information must complete the "Research on Decedent's Information Application." This application will be reviewed and approved by the IRB Chair(s), since the Common Rule does not cover research involving decedent's information. The investigators will be expected to adhere to the provisions of HIPAA. Additional information regarding research on decedent's information is detailed in the HRPP Policy and Procedure, No.6, located in Appendix N.

V. IRB MANAGEMENT OF FOOD AND DRUG ADMINISTRATION (FDA) REGULATED RESEARCH

1. Investigational Drugs, Devices, and Biologics.

The Food and Drug Administration (FDA) is a component of the U.S. Department of Health and Human Services (DHHS). The FDA's mission is to promote and protect the public health by helping safe and effective products reach the market, and then monitoring these products for continued safety while they are in use.

The FDA regulates clinical investigations (research) conducted on drugs, biologics, devices, diagnostics, and, in some cases, dietary supplements and food additives, hereinafter referred to as "FDA regulated test articles." All such investigations must be conducted in accordance with FDA requirements for informed consent and IRB review, regardless of funding source or sponsor.

When an FDA regulated test article is used in research being done at the VA or funded by another federal agency, more than one set of regulations may apply. For example, clinical trials involving FDA regulated test articles that are supported by DHHS (e.g., the National Institutes of Health) fall under the jurisdiction of both the FDA and the DHHS Office for Human Research Protections (OHRP). Such

trials must comply with the FDA and the DHHS human subject regulations as well as VA regulations and the Common Rule. Where regulations differ, the IRB should apply the stricter one.

For information regarding Investigational Devices, please refer to HRPP: Policy & Procedure No. 3, "Investigational Device Usage in Research & Development Service," in Appendix J.

a. **FDA Requirements in Relation to VA, Common Rule, and DHHS Requirements.** The human subject protection requirements found in FDA regulations are substantially the same as the VA and Common Rule requirements. However, there are important differences:

(1) The FDA has different definitions for "human subject" and "clinical investigation (research)."

FDA regulations (21CFR56.102(e)) define a human subject as "an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy individual or a patient."

FDA regulations (21CFR56.102(c)), defines clinical investigation as "...any experiment that involves a test article and one or more human subjects..." The FDA regulations further state that "...The terms research, clinical research, clinical study, study, and clinical investigation are deemed to be synonymous for purposes of this part."

The FDA definition of research in the Investigational New Drug (IND)regulations is as follows: "Clinical investigation" means any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects. For the purposes of this part, an experiment is any use of a drug except for the use of a marketed drug in the course of medical practice" (21CFR312.3(b)) Thus, under the FDA IND regulations, it is possible for one drug given to one person to be considered research.

(2) FDA has neither an assurance mechanism nor files of IRB membership. Therefore, FDA does not require the IRB or institution to report changes in membership whereas HHS does require such notification.

(3) Conditions for exemption, exception (21 CFR 50.23), and waiver (45 CFR 46.116(c) &(d) of IRB review and informed consent requirements differ.

(4) FDA regulations require specific determinations for the IRB review of device studies (see HRPP: Policy & Procedure No. 2).

(5) FDA regulations include specific requirements for reporting adverse events that are not found in VA regulations, the Common Rule, or DHHS regulations.

(6) DHHS regulations include specific additional protections for pregnant women, fetuses, and human in vitro fertilization (Subpart B); prisoners (Subpart C) and children (Subpart D) that are not contained in the VA, and Common Rule requirements. In April 2001 FDA issued regulations to protect children in research (20 CFR 50 Subpart D). In April 2001 the VA Office of Research and Development issued Directive 2001-028, requiring a centralized waiver.

In addition to regulations governing human subject protection, the FDA also has regulations governing the use of investigational drugs (21 CFR 312) and devices (21 CFR 812).

b. **Additional VA Requirements.** VA policy (M-3, Part 1, Chapter 9) requires that all research comply with the VA human subject regulations, as well as with all applicable regulations and requirements regarding storage and security procedures for investigational agents. The following applies to studies using an investigational drug, an approved drug used for an unapproved indication or an approved drug used as a comparator in a study.

(1) A VA Investigational Drug Information Record (VA Form 10-9012) must be completed by the principal investigator, submitted to the Research Service office and monitored by the Research and Development (R&D) Committee (M-3, Part 1, Chapter 9.15 b. (3)).
(2) Upon approval of the research by the IRB and R&D Committee, a Report of Subcommittee on Human Studies (VA Form 10- 1223) must be forwarded to the investigator and the Pharmacy Service.

These 2 forms (10-9012 and 10-1223) are sent to the Pharmacy Service.

c. **Research Involving Investigational FDA Regulated Test Articles.** Please see also Human Research Protection Program, Policy and Procedure No.2 “Investigational Device Usage in Research & Development Service.” Medical products, such as drugs, biologics, and medical devices need to be proven safe and effective before the FDA can approve them for sale to and use by patients. FDA reviews the results of laboratory, animal and human clinical testing to determine if the product to be put on the market is safe and effective. New medical products that have not yet been approved for marketing by the FDA require a special status so they can be legally shipped for the purpose of conducting clinical investigations to establish safety and efficacy.

(1) The IND is an investigational new drug application and is synonymous with "Notice of Claimed Investigational Exemption for a New Drug." Investigational new drug (or investigational drug) means a new drug or biological drug that is currently unapproved by the FDA for marketing is being used in a clinical investigation. An investigational drug must have an IND before it can be shipped.

(2) An approved investigational device exemption (IDE) permits a device not approved by FDA to be shipped to conduct clinical investigations of that device. Not all investigational devices need an IDE.

(3) With only a few exceptions, most clinical research being done on FDA regulated test articles with either an IND or IDE will need initial review at a convened IRB meeting.

d. **Investigator and Sponsor Responsibilities.** Under FDA regulations, the **investigator** in a clinical trial is responsible for the conduct of the study and for leading the team of individuals coordinating the study. These responsibilities include:

(1) Obtaining IRB approval and promptly report to the IRB changes in the research activity and all unanticipated risk to human subjects;

(2) Getting informed consent from each subject;

(3) Following the investigational plan;

(4) Complying fully with the regulations;

(5) Protecting the rights, welfare and safety of the subjects;

(6) Supervising the use and disposition of the test article;

(7) Maintaining accurate, current and complete records; and

(8) Disclosing relevant financial information.

The **sponsor** takes responsibility for initiating the clinical investigation, and holding the IND or IDE, but does not usually conduct the investigation. Although the sponsor is usually a pharmaceutical, biotech, or medical device company, an individual or group of individuals or medical center can also be considered a sponsor for an investigation. An investigator is referred to as the sponsor-investigator when the individual investigator is also the initiator of the clinical investigation. Some of the responsibilities of sponsors are:

(1) Selecting qualified investigators;

(2) Providing investigators with the information they need to conduct the investigation properly;

(3) Ensuring proper monitoring of the investigation;

(4) Monitoring an effective IND and IDE with respect to an investigator; and

(5) Ensuring that the FDA and (for devices) any reviewing the IRB or (for drugs) all participating investigators are promptly informed of significant new information about an investigation.

e. **IRB Review of Medical Devices.** Please see also Human Research Protection Program, Policy and Procedure No.2 “Investigational Device Usage in Research & Development Service,” in Appendix J.

f. **Radiology Devices and Radioactive Materials.** All studies involving Radiological devices or procedures are reviewed by the Radiation Safety Officer (RSO), who is a member of one IRB. Studies from the other IRB which include a radiation component are also sent to the RSO for review. The Radiation Safety Officer assures that the use of radioactivity and the conduct of procedures are appropriate.

g. **AEs and Reporting Requirements.** Some requirements for reporting AEs are the same, regardless of what sort of test article is used (e.g. a drug or a device). FDA, VA, and DHHS regulations require

prompt reporting to the IRB, FDA, OHRP, and the Office of Research Oversight (ORO) of any unanticipated problems involving risks to human subjects and others.

(1) FDA interprets "any unanticipated problems involving risks to human subjects" to mean "...an unexpected adverse experience that is not listed in the labeling for the test article. -including an event listed in the labeling ... that differs ... because of greater specificity or severity" (FR 28027).

(2) FDA interprets "...and others" to mean "...persons who are participating in clinical trials under the same or similar protocols or who may be affected by products or procedures developed in those trials" (FR 28027).

AE information submitted to the sponsor by the investigator should also be submitted to the IRB in accordance with the IRB PVAMC AE reporting policy. In addition to providing **prompt** written notification to relevant Federal agencies, including ORO (aka ORCA), FDA, and OHRP, of any unanticipated problems involving risks to subjects or others, the IRB should also report the resolution of those problems.

h. **AEs and Reporting Requirements - INDs.** FDA IND regulations (for both drugs and biologics) have requirements related to the reporting of adverse events.

(1) **Investigator Reports to Sponsor:** FDA IND regulations require that the investigator report promptly to the sponsor any "adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug. If the adverse effect is alarming, the investigator shall report the adverse effect immediately" (21 CFR 312.64(b)).

(2) **Sponsor Reports to FDA and Investigators:** FDA IND regulations require that the sponsor notify the FDA and all participating investigators of any adverse experience associated with the use of the drug or biologic that is **both** serious **and** unexpected as soon as possible but **in no event later than 15 calendar days after the sponsor determines it to be reportable,** 21CFR312.32(c)(B).

The FDA should be notified by telephone, facsimile, or in writing as soon as possible but **in no event later than 7 calendar days of the sponsor's receipt of the information of any unexpected fatal or life-threatening experience.**

"Serious adverse drug experience" is defined as "any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect," (21 CFR 312.32(a))..,

i. **AEs and Reporting Requirements - IDEs.** FDA IDE (device) reporting requirements are similar but not exactly the same as for drugs and biologics, 21CFR812.50.

(1) **Investigator to Sponsor:** FDA IDE regulations require that the investigator notify the sponsor and the IRB of any unanticipated adverse device effect **within 10 days of discovery.**

(2) **Sponsor to FDA, Investigator, and IRB.** The sponsor is required to evaluate the event and report it to the FDA, to all participating investigators, and to all reviewing the IRB **within 10 working days of the sponsor's receipt of the information.**

j. **"Off-label" (Unapproved) Use of FDA-Regulated Products in Medical Practice.** The FDA approves the sale, use, and labeling of a product for specific indications (the reason the product is being used - a disease, condition, as a diagnostic tool, etc.). "Off-label" or unapproved use is when the product is used in a way or on a population different from that for which it was approved. The IND regulations do not apply to the use of marketed drugs for unlabeled indications in the practice of medicine (21 CFR 312.2(d)).

k. **"Off-label" (Unapproved) Use of FDA Regulated Products in Research.** Good medical practice and the best interests of the patient require that physicians use legally available, marketed drugs, biologics and devices according to their best knowledge and judgment. If physicians use a product for an indication not included in the approved labeling (i.e., off-label), they have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects.

The off-label use of a marketed drug or biologic in **research** does require IRB review, informed consent and, under some circumstances, may require an IND. To be exempt from the requirements of the IND regulations, all of the following must apply (note that this includes the requirement of IRB review and informed consent):

(1) The investigation is not intended to support of a new indication for use nor any other significant change in the labeling for the drug;

(2) The investigation is not intended to support a significant change in the advertising for the product;

(3) The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;

(4) The investigation is conducted in compliance with the requirements for institutional review board review and informed consent; and

(5) The investigation is conducted in compliance with the FDA regulations on promoting and charging for investigational drugs (21 CFR 312.7).

Use of an off-label marketed product in research intended to support **a new indication for use, change in labeling or advertising** requires IRB review, informed consent and submission of an IND.

Using an off-label marketed product in research involving a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with its use requires IRB review, informed consent and may also require submission of an IND.

1. **Expanded Access to Investigational Drugs.** Investigational products are sometimes used for treatment of serious or life-threatening conditions either for a single subject or for a group of subjects. The procedures that have evolved for an investigational new drug (IND) used for these purposes reflect the recognition by the FDA that, when no satisfactory alternative treatment exists, subjects are generally willing to accept greater risks from test articles that may treat life-threatening and debilitating illnesses. The following mechanisms expand access to promising therapeutic agents without compromising the protection afforded to human subjects or the thoroughness and scientific integrity of product development and marketing approval (21 CFR 312.34, 312.35, and 312.83).

(1) **Open Label Protocol or Open Protocol IND.** These are usually uncontrolled studies, carried out to obtain additional safety data (*Phase III studies*). They are typically used when the controlled trial has ended and treatment is continued so that the subjects and the controls may continue to receive the benefits of the investigational drug until marketing approval is obtained. These studies require prospective IRB review and informed consent.

(2) **Treatment IND.** The treatment IND (21 CFR 312.34 and 312.35) is a mechanism for providing eligible subjects with investigational drugs for the treatment of serious and life-threatening illnesses for which there are no satisfactory alternative treatments. A treatment IND may be granted after sufficient data have been collected to show that the drug "may be effective" and does not have unreasonable risks. Because data related to safety and side effects are collected, treatment INDs also serve to expand the body of knowledge about the drug. Four requirements must be satisfied before a treatment IND can be issued:

(a) The drug must be intended to treat a serious or immediately life threatening disease;

(b) There must be no satisfactory alternative treatment available;

(c) The drug must already be under investigation or the drug trials must have been completed; and

(d) The trial sponsor must be actively pursuing marketing approval.

Treatment IND studies require prospective IRB review and informed consent.

(3) **Parallel Track Studies.** FDA also permits wider access to promising new drugs for HIV/AIDS related diseases under a "separate access" protocol that "parallels" the controlled clinical trials that are essential to establish the safety and effectiveness of new drugs. These so-called "parallel track" studies require prospective IRB review and informed consent.

m. **Expanded Access to Investigational Devices.** Please see also Human Research Protection Program, Policy and Procedure No.2 “Investigational Device Usage in Research & Development Service,” in Appendix J. According to statute and FDA regulations, an unapproved medical device may normally only be used in human subjects when the device is under clinical investigation and when used by investigators participating in the clinical trial. FDA recognizes, however, that there may be

circumstances under which a health care provider may wish to use an unapproved device to save the life of a patient, to prevent irreversible morbidity or to help a patient suffering from a serious disease or condition for which there exists no alternative therapy. Four main mechanisms are utilized by FDA to make unapproved devices available to patients/physicians faced with circumstances such as those described above. These mechanisms are consistent with the Expanded Access provisions of the FDA Modernization Act of 1997 (Section 561 of the Federal Food, Drug, and Cosmetic Act). The sponsor must agree and FDA must approve the use. Under most circumstances such studies require IRB review and informed consent.

(1) **Emergency Use** - Regulatory Authority: 50 FR 42866 and 21 CFR 812.35(a) and "Guidance for the Emergency Use of Unapproved Medical Devices."
Criteria for use under this expanded access mechanism includes that the subject must 1) have a life-threatening condition; 2) no alternative is available and 3) no time to obtain FDA approval of the device. This may be used before or after initiation of a clinical trial. Access is limited to a few patients. FDA approval of use of the investigational device is not required prior to use. After the device is used a report should be submitted to the FDA. The necessary patient protection measures that must be followed include: 1) independent assessment by an uninvolved doctor; 2) IRB chairperson's concurrence; 3) institutional clearance from the Chief of Staff or his designee; 4) informed consent.

(2) **Treatment Use/IDE –** Regulatory Authority: **21 CFR 812.36.**
Criteria for use under this expanded access mechanism includes that the subject must 1) have a life-threatening condition or serious disease; 2) no alternative available and 3) the device is being used in a controlled clinical trial and 4) the sponsor is pursuing marketing approval. This may be used only during a clinical trial. Access is available widely, depending on the patient and physician needs. FDA approval of use of the investigational device is required prior to use. FDA approval is obtained via a Treatment Investigational Device Exemption (IDE) supplement with: 1) intended Use, protocol, and patient selection criteria; 2) rationale for treatment use; 3) methods used to evaluate devices use and minimize risks; 4) monitoring plan; 5) summary of safety and efficacy data; 6) instructions for use and device labeling; 7) commitment to patient protection; 8) investigator agreement; and 9) the price if it will be sold. The necessary patient protection measures that must be followed include: 1) IRB approval and 2) informed consent.

(3) **Continued Access to Investigational Devices –** Regulatory Authority: "Continued Access to Investigational Devices During PMA Preparation and Review" and ODE Blue Book IDE Memorandum #D96-1.
This mechanism allows access to a device while a marketing application is being prepared and reviewed, and can be used to collect additional evidence of safety and effectiveness, as well as to address new questions regarding the investigational device, such as labeling claims.
Criteria for use under this continued access mechanism includes that there must be: 1) a public health need for the device and 2) preliminary evidence that the device is effective and there are no significant safety concerns. This may be used only after the completion of a clinical trial. The number of patients that may be treated is the same rate of enrollment as study. FDA approval of use of the investigational device

is required prior to use. FDA approval is obtained via a Investigational Device Exemption (IDE) supplement with: 1) justification for extended study; 2) summary of safety and efficacy data and risks posed by the device; 3) proposed enrollment rate; 4) clinical protocol; and 5) progress towards marketing approval. The necessary patient protection measures that must be followed include: 1) IRB approval and 2) informed consent.

(4) **Compassionate Use –** Regulatory Authority: 21 CFR 812.35(a)
Criteria for use under this expanded access mechanism includes that the subject must have a serious condition/disease with no alternative intervention available. Compassionate use may be used only during the conduct of a clinical trial. Access is limited to an individual patient or a small group of patients. FDA approval of use of the investigational device is required prior to use. FDA approval is obtained via a Investigational Device Exemption (IDE) supplement with: 1) explanation of circumstances constituting need for the device; 2) reasons alternatives are not acceptable; 3) deviations from protocol, if any; and 4) patient protection measures. The necessary patient protection measures that must be followed include: 1) independent assessment by an uninvolved doctor; 2) IRB chairperson's concurrence; 3) institutional clearance from the Chief of Staff or his designee; 4) informed consent

Stated in the U.S. Department of Health & Human Services, Guidance on IDE Policies and Procedures (p. 18) is "As a matter of practice, FDA has expanded the criteria of "life-threatening condition" to include serious diseases or conditions such as sight-threatening and limb-threatening conditions as well as other situations involving risk of irreversible morbidity. This is consistent with the new law."

n. **Gene Transfer Research**. Gene transfer involves the administration of genetic material to alter the biological properties of living cells for therapeutic use. Gene transfer activities in humans are investigational and are regulated by the both the FDA and the National Institutes of Health (NIH) Office of Biotechnology Activities (OBA).

(1) FDA regulations require the submission of an IND for human gene transfer research through the FDA Center for Biologics.

(2) DHHS regulations specify that no individual may be enrolled in human gene transfer research until review has been completed by the NIH Recombinant DNA Advisory Committee (RAC), local Institutional Biosafety Committee (IBC) approval has been obtained, local IRB approval has been obtained, and the investigator has obtained all other regulatory authorizations from the subject (FR 196, October 10, 2000).

(3) While the RAC is advisory to the Director of the NIH, compliance with RACs guidelines is mandatory for all investigators at institutions that receive NIH funds for research involving recombinant DNA.

o. **Emergency Use of a Test Article Without IRB Review.** Please see also Human Research Protection Program: Policy and Procedure No. 2, "Investigational Device Usage in Research & Development Service," in Appendix K for information regarding the emergency use of investigational devices.

An exemption under FDA regulations at 21 CFR 56.104(c) permits the emergency use of an investigational drug, or biologic on a one-time basis per institution without IRB review and approval. The first three of the following conditions must be met for this type of emergency use:

(1) A human subject is in a life-threatening situation.

(2) No standard acceptable treatment is available.

(3) There is insufficient time to obtain IRB approval.

(4) The emergency use must be reported to the IRB within five working days. This reporting must not be construed as an approval for the emergency use by the IRB.

(5) Ordinarily, the investigator must obtain the informed consent of the subject for such an emergency use, except as described below.

VA policy M-3, Part 1, Chapter 9.15(f)(2)(a) requires separate authorization from the Chief Medical Director for patients outside a research protocol for each such emergency use of a test **article without IRB review**, as well as the filing of VA Form 10-9012, Investigational Drug Information Record with the Pharmacy Service.

p. **Waiver of Informed Consent Under Compassionate Use or on an Emergency Basis** Please see also Human Research Protection Program: Policy and Procedure, No. 2, "Investigational Device Usage in Research & Development Service." **Note:** Even in an emergency situation, the investigator is required to obtain informed consent of the subject or the subject's legally authorized representative unless both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing all of the following [21 CFD 50.23 (a)].

An exception under FDA regulations at 21 CFR 50.23 permits the emergency use of an investigational drug, device, or biologic without informed consent where the investigator and an independent physician who is not otherwise participating in the clinical investigation certify in writing all four of the following specific conditions:

(1) The subject is confronted by a life-threatening situation necessitating the use of the test article;

(2) Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from the subject and there is a medical emergency or urgency.

(3)Time is not sufficient to obtain consent from the subject's legally authorized representative and there is a medical emergency or urgency.

(4) No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life and there is a medical emergency or urgency.

If time is not sufficient to obtain the independent physician determination before use of the test article, the actions of the investigator must be reviewed and evaluated in writing by an independent physician within 5 working days. The emergency use must be reported to the IRB within 5 working days. This reporting must not be construed as an approval for the emergency use by the IRB. (Note: This use without prospective IRB approval is not research, but medical treatment, and cannot be counted as research data.)

q. **"Compassionate" or "Humanitarian" Use of a Test Article.** Questions frequently arise regarding "compassionate" or "humanitarian" use of a test article. "Compassionate use" and "humanitarian use" are not terms that appear in the VA, or DHHS regulations or the Common Rule. "Compassionate use" and "humanitarian use" are often meant to refer to the emergency use situations discussed above.

r. **Humanitarian Use Device (HUD)**
The FDA defines humanitarian use device: "is a device that is intended to benefit patients in the treatment and diagnosis of diseases or conditions that affect or is manifested in fewer than 4,000 individuals in the United States per year." U.S. Food and Drug Administration – Center for Devices and Radiological Health, Humanitarian Device Exemption (HDE) Regulation Questions and Answers; Final Guidance for Industry, July 12, 2001.

A HUD requires a Humanitarian Device Exemption (HDE) for the FDA. A HDE is an application that is similar to a pre-market approval (PMA) application, but exempt from the effectiveness requirements of a PMA. An approved HDE authorizes marketing of a Humanitarian Use Device (HUD).

FDA regulations (21 CFR 814.124(a)) require the IRB to conduct a full board review of a HUD prior to it's use, except in emergency situations in which the physician determines that approval cannot be obtained in time to prevent serious harm or death to the patient. An investigator who would like to use a HUD, must forward a letter of request to the IRB. Effective January 2003, the clinician/investigator must also submit the Proposed Project Questionnaire (PPQ), protocol and any other additional information requested. The convened full board IRB will review and make a determination of the use of the HUD at the PVAMC. However, the IRB does not have to approve individual uses of the HUD if it is within the FDA approved indication.

The HDE regulations do not require the use of informed consent because the HDE provides for marketing approval and so use of the HUD does not constitute research or an investigation, which would normally require informed consent. In these cases, the clinician/investigator must provide a copy of the clinical consent to be used to the IRB. However, if the HUD is the subject of a clinical investigation (the HDE holder is collecting safety and effectiveness data to support a PMA under the approved HDE) IRB approval and informed consent are required (21 CFR Parts 56 and 50).

If the IRB approves the use of the HUD, the HUD will be reviewed on an annual basis by the IRB. The continuing review of the HUD may be performed under an expedited process. The HUD will be tracked in the MIRB database.

The HUD Review Process flowchart may be found in Appendix N.

s. **Requirements for Planned Emergency Research (21CFR50.24)**
The PVAMC may not review and conduct planned emergency research, according to the VA Office of Research Oversight (ORO), formally known as the Office of Research Compliance & Assurance (ORCA). Please see Appendix R for the related documentation.

Questions regarding the PVAMC IRB SOP may be directed to:

Dennis Mazur, M.D., Ph.D., IRB Chair

Sola Whitehead, C.I.P., IRB Coordinator

Angela Lacey, Research Assurance & Compliance Coordinator

Further information about the Research Program and the Human Research Protection Program may be found on the PVAMC Research & Development Home Page, accessed through the following link: http://www.visn20.med.va.gov/portlandrd/index.html.